Sudan University of Science and Technology

College of Graduate Studies

Evaluation of Pregnancy in Patients with Hypertension and Diabetes Using Ultrasonography

تقويم الحمل في النساء المصابات بالسكر والضغط باستخدام الموجات فوق الصوتية

A thesis submitted for the fulfillment of PhD degree in Medical Diagnostic Ultrasound

By: *Safa Anis Hassan Mahmoud*

Supervised by: *Dr: Mohamed Elfadel Garelnabi*

Co Supervisor: *Dr: Mona Ahmed M.Ahmed*

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الآية

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الذاريات الاية 21

Dedication

To my mam (Nafisa Alhaj) whom I love very much more than anyone in my life.

To my father who always encourages me to go forward.

T0 my very help full husband Sohaib.

To my kids Ola, Lina, and Ahmed, whom I love so much.

To my sister Dr: Ola, and brothers Mohamed, Mustfa and Dr: Ashraf Alhassan.

To my best friends Myson Wansy, Nisreen Hassan, Safa Zaroug.

To all those whom I love.

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List of Content

List of Figure

List of Tables

List of Abbreviations

HT	Hypertension
BHT	Blood hypertension
CRL	Crown rump length
AGA	Angiotensin-converting enzyme.
A11RAs	Angiotensin-11-receptor antagonists.
BMI	Body mass index
GRH	Gonadotropin releasing hormone
FST	Follicular –stimulating hormone
LH	Luteinizing- hormone
FGF8	Fibroblast growth factor 8
CRL	Crown rump length
CNS	Central nervous system
RDS	Respiratory distress syndrome
Hcg	Human chorionic gonadotropin
VACTRL	Vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies.
DM	Diabetes mellitus
TEFs	Tracheoesophageal fistula
ADPKD	Autosomal dominate poly cystic kidney disease
KHz	Kilo hers
AFV	Amniotic fluid volume
PGD	Pregestational diabetes mellitus
IUFD	Intrauterine fetal death

Abstract

Ultrasound has big values in scanning fetus, and early detecting of any abnormal status during pregnancy even for fetus or mother.

The research was conducted to correlate between the incidence of abortion, IUFD, fetal anomalies, as well as placenta site abnormalities and amniotic fluid volume abnormalities in diabetic (DM) and hypertensive (HT) pregnant women in Sudan in Khartoum City using ultrasonography.

The research was prospective, analytic study was conducted from October 2015 to May 2019, and included 143 pregnant patients with diabetes and hypertension, presenting during this period to the ultrasound department in Medical Corp Hospital. Pregnant women were scanned by ultrasound to assess the pregnancy status concerning the previous concerns, in the second and third trimester. The scan was done using tow dimensional Mindary machine. The data descriptive was analyzed and measured the different variables in the research and determine the relationship between them.

The patients were distributed in three age groups and were between less than 20 and 43 years old. The 1st group was 25 years and less representing (25.9%) of sample, the 2ed group (26-40) representing (67.8%) of sample, the 3ed group 40years and above was (6.3%) of sample. The second group was represented the bearing age in Sudan. The patients who have GD were (28.7%). And (21%) with PGD, (49.7%) have HT, (0.7) has HT and DM.

Some of patient have family history of DM, and HT and this presenting (66.4) of sample, and (33.6%) haven't. (12%) of sample undergo a previous IUFD due to DM or HT, (88%) haven't. There was (6.3%) of patients have fetus with anomalies, and this was due to DM, or HT. The anomalies were (2.1%) microcephaly, (0.7%) anencephaly, (0.7%) fetal ascites, (2.1%) spina bifida, (0.7%) hydrocephalus, (0.7%) undescended testes. (2.1%) have low laying placenta. (0.7%) has abruption placenta, (92.3) have normal placenta site. (87.4) of sample have normal AFV, where (6.3%) have polyhydramnios, while (6.3%) have oligohydramnios.

As a conclusion to the research, majority of women who have DM/HT can undergo normal pregnancy and outcomes, but some of them might encounter complications with intrauterine fetal death, fetal congenital malformations and anomalies, and stillbirth. The incidence rate of these problems is increased with increasing maternal age.

ملخص البحث

تعد الموجات الصوتية اداة قيمة في مسح الجنين واكتشاف اي خلل اثناء الحمل للجنين والام معا. تم اجراء البحث لتقييم النساء الحوامل المصابات بالضغط والسكر لمعرفة الاثار الناتجة عنهم بالنسبة للمرأة الحامل والجنين باستخدام فحص الموجات فوق الصوتية في جمهورية السودان في ولاية الخرطوم في العاصمة مدينة الخرطوم. الدراسة بدأت من شهراكتوبر2015 حيث تم المسح في الثلثين الثاني والثالث من الحمل الي مايو 2009 ل 143 امراة في المستشفي العسكري. تم عمل المسح باستخدام الموجات فوق الصوتية باستخدام جهاز موجات فوق الصوتية ذي بعدين لمتابعة نبض الجنين والسائل الامنيوسي. موقع المشيمة في جدار الرحم. العيوب الخلقية. وحالات الاجهاض السابقة نتيجة الضغط او السكر. وحالات موت الجنين داخل الرحم ايضا نتيجة الضغط او السكر كانت النتائج كالاتي: اولا تم تقسيم المرضي الي ثلاث فئات عمرية الاولي من عمر25 سنة واقل وكانت تمثل (25.9%). الفئة العمرية الثانية من عمر 26- 40 سنة وكانت تمثل (66.8%) والثالثة تمثل (6.3%) اكثر من 40 سنة. الفئة العمرية الثانية كانت الفئة ذات المرضي الاكثر أي هي عمر الحمل والانجاب ف السودان. (6.3%) من المرضي كان لهم اجنة بها عيوب خلقية منها عيوب في الراس والنخاع الشوكي (2.1%) وخصية معلقة واستسقاء بنسبة (0.7%).

كان هناك نسبة (28.7%) من المرضي مصابات بسكر الحمل. و21% مصابات بداء السكر من النوع الثاني و (49.7%) مصابات بالضغط ومريضة واحدة مصابة بالضغط والسكر معا وتمثل (0.7%) من العينة. (6.3%) لهم نقص ف السائل الامنيوسي ومثلهم له زيادة فيه. (2.1%) من المريضات لهم مشيمة متقدمة.

(12%) منهم حدث لهم موت للجنين ف الثلث الاخير من الحمل نتيجة الضغط او السكر.

خلص البحث الي ان اغلب النساء المصابات بالضغط والسكر اثناء الحمل يمكن ان يحظين بحمل طبيعي ونتيجة حمل طبيعية ولكن بعضهن يتعرضن لحمل مع مضاعفات وايضا ولادة مع مضاعفات. لذا نوصي

بضـرورة تـوفر الرعايـة الصـحية الأوليـة للنسـاء قبـل الحمـل واثنائـه الـي الـولادة لتجنـب الاثـار والمضـاعفات الناتجة عن الضغط والسكر.

Chapter one

Introduction

1.1 Introduction:

Pregnancy is 280 days, 40 weeks, or 9 months. It divided in to three periods, the first period is first trimester which begins from first week to 12 weeks through which the oogenesis is going on. The second period is the second trimester which begins from 13 to 26 weeks, and the last period is the third trimester which begin from 27 till delivery. Pregnancy is a serious duration for mother and fetus due to several problems and complications that may occur to both during this period. These problems such as diabetes mellitus, gestational diabetes, hypertension and induced hypertension. These problems leading to reverse outcome even for mother and fetus such as abortions, mal formations, pre-eclampsia, intrauterine fetal restrictions. (T.W Sadler 2012)

Many researches and studies in several years are going on this way to find out the complications and relation between these conditions and the delivery outcome.

Ultrasound plays a big rule in assessing fetus during pregnancy. It is an easy none invasive procedure through which pregnancy can be assessed. It used to confirm pregnancy in first trimester even positive or negative, gestational age, number of gestational sacs, expected delivery date, and scanning for fetal anomalies, gender, in second trimester, and amniotic fluid volume, placenta site and placenta maturation, in the third trimester.

1.2 Problem of the study:

Pregestational hypertension, pregestational diabetes (PGD), gestational diabetes (GDM), and induced hypertension are the most common and of high risks diseases which lead to reverse outcome of pregnancy to even mother and fetus. They increased the mother morbidity, and mortality, or may lead to eclampsia, and pre-eclampsia, also mother can undergo diabetes mellitus (DM), or hypertension (HT) in future. Fetus can be complicated with abortion, intrauterine fetal death, malformation and congenital anomalies. Also, pregnancy can be complicated with placenta site abnormalities, and amniotic fluid abnormalities. So, assessing using ultrasound is very predicting to know how the pregnancy is going on.

1.3 Hypothesis:

Diabetes mellitus (DM) and hypertension (HT) can cause to fetus during pregnancy abortions, intrauterine fetal death, polyhydramnios, oligohydramnios, fetal anomalies, and placenta site abnormalities.

1.4 Objectives:

General objective: The general objective of this study is to evaluate pregnancy in hypertensive and diabetic pregnant women, and detection of complications which are associated with DM/HT, using ultrasound.

Specific Objective:

- To determine the placenta site in diabetic and hypertensive pregnant women.
- To evaluate the amniotic fluid volume.
- To detect abortions and intrauterine fetal death.
- To count the incidence of fetal anomalies.
- To correlate between age of mother and incidence of DM/HT.
- To correlate between mother age, and DM/HT complications in fetus.
- To correlate between having a family history of DM/HT and incidence of abortion, intrauterine fetal death, fetal anomalies and malformations in fetus.

1.5 Inclusion Criteria:

- Diabetic or hypertensive pregnant woman.
- Single pregnancy.
- Second and third trimester.

1.6 Exclusion Criteria:

- Non diabetic or nonhypertensive pregnant woman.
- Multiple gestation (twins, triple, or more pregnancy).
- First trimester.

1.7 Significance of the Study:

This study will highlight the significance of U/S to be utilized as an early diagnosis and predictor for the complications of hypertension and diabetes in pregnancy.

1.8 Overview of the Study:

This study will fall into five chapters, chapter one is an introduction which includes the problem of the study, exclusion, and inclusion criteria, objectives, significance of the study and overview. While chapter two contains scholar literature about the problem of the study. Chapter three includes the material used to collect the data and method of data collection. Chapter four includes results presentation using tables and figures, and finally chapter five will present discussion of the presented results as well as conclusion and recommendations.

Chapter Tow

Literature Review

2.1 Hypertension:

Blood pressure is the force exerted by the blood against the walls of blood vessels, and the magnitude of this force depends on the cardiac output and the resistance of the blood vessels.

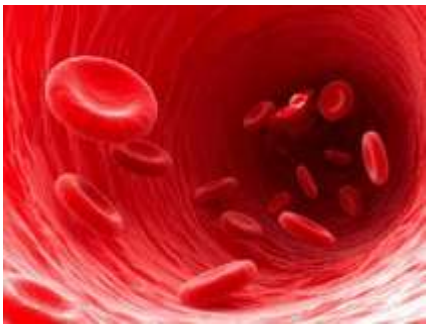


Figure (2.1) The blood flowing inside vessels exerts a force against the walls - this is blood pressure (Markus Mac Gill, April 2016*)*

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure. About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors. Lifestyle factors that increase the risk include excess salt, smoking, and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such

as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills. Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively. Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic. High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children. Ambulatory blood pressure monitoring over a 24 hour period appears more accurate than office best blood pressure measurement. (Markus Mac Gill, April 2016*)*

Systolic: The pressure as the heart pumps blood around the body, given first, while diastolic is pressure as the heart relaxes and refills with blood, given second.

2.1.1 Signs and Symptoms of Hypertension:

Hypertension is rarely accompanied by symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with high blood pressure report headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. (Markus Mac Gill, April 2016*).*

2.1.2 Type of Hypertension:

2.1.2.1 Crisis Hypertension: Severely elevated blood pressure equal to or greater than a systolic of 110, sometimes termed malignant or accelerated hypertension

2.1.2.2 Primary Hypertension: Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure. Blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Several environmental factors influence blood pressure. High salt intake raises the blood pressure in salt sensitive individuals; lack of exercise, obesity, and depression can

play a role in individual cases. The possible role of other factors such as caffeine consumption, and vitamin D deficiency are less clear. Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), is also thought to contribute hypertension. Events in early life, such as low birth weight, maternal smoking, and lack of breast feeding may be risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain unclear.(Markus Mac Gill, April 2016*)*

2.1.2.3 Secondary Hypertension: Secondary hypertension results from an identifiable cause. Kidney disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions, such as Cushing syndrome, hyperthyroidism, hypothyroidism, hyper aldosternism syndrome, hyperparathyroidism. Also sleep apnea, obesity, pregnancy, coarctation of aorta. (Markus Mac Gill, April 2016*)*

2.1.2.4 Resistant Hypertension: Resistant hypertension is defined as hypertension that remains above goal blood pressure in spite of using, at once, three antihypertensive medications belonging to different drug classes. Low adherence to treatment is an important cause of resistant hypertension. Resistant hypertension may also represent the result of chronic high activity of the autonomic nervous system; this concept is known as "neurogenic hypertension". (Markus Mac Gill, April 2016*)*

2.1.2.5 Children Hypertension: Hypertension occurs in around 0.2 to 3% of newborns; however, blood pressure is not measured routinely in healthy newborns. Hypertension is more common in high risk newborns. A variety of factors, such as gestational age, post conceptional age and birth weight needs to be taken into account when deciding if a blood pressure is normal in a newborn. (Markus Mac. April 2016*).*

Table (2.1) Classification of blood hypertension in adult (JNC7):

Category	Systolic mm Hg	Diastolic mm Hg
Normal	90-119	60-79
High normal prehypertensive	120-139	80-89
Stage 1 HT	140-159	90-99
Stage 2 HT	160-179	100-109
Stage 3 HT emergency HT	≥180	≥110
Isolated systolic HT	≥140	<90

Blood pressure is normally distributed in the population and there is no natural cut-off point above which 'hypertension' definitively exists and below which it does not. The risk associated with increasing blood pressure is continuous, with each 2 mmHg rise in systolic blood pressure associated with a 7% increased risk of Mortality from ischemic heart disease and a 10% increased risk of mortality from stroke. In any individual person, systolic and/or diastolic blood pressures may be elevated. Diastolic pressure is more commonly elevated in people younger than 50. With ageing, systolic hypertension becomes a more significant problem, as a result of progressive stiffening and loss of compliance of larger arteries. At least one quarter of adults (and more than half of those older than 60) have high blood pressure. (Markus Mac Gill, April 2016*)*.

2.1.3 Hypertension & Pregnancy:

Hypertension occurs in approximately 8–10% of pregnancies. Two blood pressure measurements six hours apart of greater than 140/90 mm Hg is considered diagnostic of hypertension in pregnancy. High blood pressure in pregnancy can be

classified as pre-existing hypertension, gestational hypertension or pre-eclampsia. (Markus Mac Gill, 2016*)*.

2.1.4Classification of Hypertension During Pregnancy:

2.1.4.1Pre-existing hypertension: Pre-dates pregnancy or appears before 20 weeks, and gestational hypertension appears at or after 20 weeks. (Markus Mac Gill, 2016*)*.

2.1.4.2Gestational hypertension: Define as hypertension appears at or after 20 wks. It is defined as systolic blood pressure≥140mmHg and/or diastolic blood pressure ≥90mmHg in a previously normotensive pregnant woman who is ≥20 week of gestation and has no proteinurea. The blood pressure readings should be documented on at least two occasions at least six hours apart. It is considered severe when sustained elevations in systolic blood pressure >160mmHg and/or diastolic blood pressure ≥110mmHg are present for at least six hours Preeclampsia, a human-pregnancy-specific disease defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation, occurs in about 2–8% of pregnancies. Gestational hypertension is one of several causes of hypertension in pregnant women. It occurs in about 6 % of pregnancies. It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide, and it is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually. Thus, reducing maternal mortality by 75% between 1990 and 2015 has been considered as part of the millennium development goals of the WHO Nations. (Samina et al, 2015).

2.1.4.3Pre-eclampsia in women with pre-existing hypertension is defined as resistant hypertension, new or worsening proteinuria, or one or more adverse conditions noted below. Resistant hypertension is elevation in blood pressure after

20 weeks gestation that requires three antihypertensive medications to control it. In women with gestational hypertension, preeclampsia is defined as new-onset proteinuria *or* one or more adverse conditions. Edema and weight gain have been excluded from the definition of preeclampsia. (Perinatal manual of Southwestern Ontario March, 2011).

2.1.5 Mother Complications:

- Vascular/Pulmonary complications: Systolic BP > 160 mmHg or diastolic BP > 110mmHg, pulmonary edema, chest pain Dyspnea.
- Renal complications: serum creatinine, serum albumin (< 20g/L), Proteinuria. (Perinatal manual of Southwestern Ontario March, 2011)

- Hepatic: elevated AST, ALT, LDH, Severe nausea / vomiting, Persistent abdominal or right upper quadrant pain, Jaundice.
- Hematologic: platelets <100,000, Disseminated intravascular coagulopathy (DIC). (Perinatal manual of Southwestern Ontario March, 2011)
- CNS: persistent new or unusual headache, visual disturbances, hyper reflexia, seizures, stroke (may occur with a systolic BP > 160 mmHg).
- HELLP Syndrome: hemolysis, low Platelets, elevated liver enzymes. (Perinatal manual of Southwestern Ontario March, 2011)

2.1.6 Fetal Complications:

- Oligohydramnios.
- Absent or reversed end-diastolic umbilical artery flow as indicted by Doppler flow studies.
- Atypical / abnormal fetal heart rate.
- Placental abruption.
- Prematurity.
- Intrauterine death. (Perinatal manual of Southwestern Ontario March, 2011)

2.2 Diabetes Mellitus:

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar, or glucose), or when the body cannot effectively use the insulin it produces. Diabetes is an important public health problem, one of four priority non communicable diseases (NCDs) targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. (World Health Organization, 2016).

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. This reflects an increase in associated risk factors such as being overweight or obese. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries. (World Health Organization, 2016).

Diabetes caused 1.5 million deaths in 2012. Higher-than-optimal blood glucose caused an additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Forty-three percent of these 3.7 million deaths occur before the age of 70 years. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries. (Word Health Organization, 2016).

Because sophisticated laboratory tests are usually required to distinguish between type 1 diabetes (which requires insulin injections for survival) and type 2 diabetes (where the body cannot properly use the insulin it produces), separate global estimates of diabetes prevalence for type 1 and type 2 do not exist. The majority of people with diabetes are affected by type 2 diabetes. This used to occur nearly entirely among adults, but now occurs in children too. (Word Health Organization, 2016).

Diabetes in pregnancy was first described by Bennewitz in Germany (1826). He described a woman with recurrent glycosuria and intense thirst in 3 successive pregnancies. In 1967, the term "gestational diabetes" was probably first used by Jorge Peterson in Copenhagen. The discovery of insulin in 1921, by Banting and Best changed the outlook for the pregnant diabetic patient completely.1-4 GDM is defined as carbohydrate intolerance of variable severity with onset or first diagnosed during pregnancy.5 The definition was first accepted in the First International Workshop. (Maxima Anand et al, 2017)

Clinical classification of diabetes mellitus in pregnancy:

- Type 1 or insulin dependent diabetes mellitus.
- Type 2 or non-insulin dependent diabetes mellitus. (Maxima Anand et al, 2017)

2.2.1 Types of Diabetes:

2.2.1.1 Type 1 Diabetes: Is heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both cohorts. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with DKA. The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the true diagnosis become more obvious over time. (William T. Cefalu, January 2017).

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of b-cell autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit

varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may be intermittent. (William T. Cefalu, January 2017).

Autoimmune destruction of b-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis. Patients with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves' disease, Addison disease, celiac disease, autoimmune hepatitis, myasthenia gravis, and pernicious anemia. (William T. Cefalu, January 2017).

2.2.1.2 Type 2 Diabetes: The most common type of diabetes, is a disease that occurs when blood glucose, also called blood sugar, is too high. Blood glucose is main source of energy and comes mainly from the food individual eat. Insulin, a hormone made by the pancreas, helps glucose get into cells to be used for energy. In type 2 diabetes, body doesn't make enough insulin or doesn't use insulin well. Too much glucose then stays in blood, and not enough reaches the cell. (Rita Basu et al, May 2017).

Type 2 diabetes can develop at any age, even during childhood. However, type 2 diabetes occurs most often in middle-aged and older people. It is more likely to develop type 2 diabetes if age is 45 or older, have a family history of diabetes, or overweight or obese. Diabetes is more common in people who are African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander. (Rita Basu et al, May 2017).

Physical inactivity and certain health problems such as high blood pressure affect the chances of developing type 2 diabetes. Also more likely to develop type 2 diabetes if there is prediabetes or gestational diabetes during pregnancy. (Rita Basu et al, May 2017).

Symptoms of diabetes include, increased thirst and urination, increased hunger, feeling tired, blurred vision, numbness or tingling in the feet or hands, sores that do not heal, unexplained weight loss. Symptoms of type 2 diabetes often develop slowly over the course of several years and can be so mild that you might not even notice them. Many people have no symptoms. Some people do not find out they have the disease until they have diabetes-related health problems, such as blurred vision or heart disease. (Rita Basu et al, May 2017).

Type 2 diabetes is caused by several factors, including overweight and obesity ,not being physically active, insulin resistance.(Rita Basu et al, May 2017).

2.2.1.3 Type 3 diabetes: Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Incidence of GDM is increasing worldwide for recent trends in obesity and advancing maternal age, with huge healthcare and economic costs Women exposed to GDM are at high risk for pregnancy complications, future type 2 diabetes mellitus (DM), and cardiovascular disease. In particular, several lines of evidence indicate a continuum of risk for adverse pregnancy outcomes for mothers and their offspring's related to increasing maternal glucose levels, whereas treatment to reduce maternal glucose levels reduces this risk.(Carmelo Capula et al, 2013)

Gestational diabetes (GDM), which diagnosed during pregnancy. The diagnostic criteria for (GDM) remain controversial; however, the committee has chosen a preferred approach and an alternate approach. The preferred approach is to being with 50g glucose challenge test and, if appropriate, proceed with a 75g oral glucose tolerance test making the diagnosis of GDM if more or equal 1 value is abnormal (fasting more or equal 5.3mmol/L, 1 hour more or equal 10.6mmol/L, 2hour more or equal 9.0mmol/L).the alternate approach is a 1-step approach of a 75g oral glucose tolerance test, making the diagnosis of GDM if more or equal 1value is abnormal (fasting more or equal 5,1mmol/L, 1hour more or equal

10.0mmol/L, 2hour more or equal 8.5mmol/L). Untreated GDM leads to increased maternal and perinatal morbidity, while treated is associated with outcome similar to control population. (David Thompson M et al, 2013)

2.2.2 Fetal Adverse Outcomes:

Pregnancy loss is significantly higher among women with diabetes compared to the nondiabetic population. Recently, a population-based cohort study conducted in the UK by Casson et al, has reported that women with type 1 diabetes have a higher risk of late fetal loss, presenting a four- to five-fold increase in perinatal death, and a four- to six-fold in stillbirth compared to the general population. Neonatal mortality is also higher among infants of diabetic mothers in approximately 15-fold when compared to the general population Schaefer et al. have found a two-fold increase in the risk of congenital anomalies when fasting glucose levels are already greater than 120 mg/dL when first detected during pregnancy. The increased risk of congenital abnormalities found in diabetic mothers seems to be associated to poor metabolic control during the period of organogenesis that occurs in the first trimester of pregnancy probably due to the negative impact of a hyperglycemic milieu in the growing fetus. (Carlos Antonio Negrato et al, 2012)

The pathogenesis of congenital malformations of all types, which have four to ten times higher incidence in pregnant women with diabetes, is very complex and has possibly a multifactorial origin. A strong link between hyperglycemia and malformations has been established, but the precise mechanism by which it occurs has not been completely elucidated. It is supposed that hyperglycemia could cause damage to the developing yolk sac, an increased production and liberation of free oxygen radicals, deficiency of myoinositol and arachidonic acid and a disruption in signal transduction; increasing evidences suggest that embriopathies might be connected to a disruption in intracellular signaling by inositol-derived effectors and prostaglandin precursors such as arachidonic acid. Also, a as a result of the presence of these fuels, some type of genotoxic effect might occur which could

cause morphologic damages in the fetus. (Carlos Antonio Negrato et al, 2012)

2.2.3 Maternal Adverse Outcomes:

On the maternal side, morbidity and mortality rates are also higher among pregnant women with diabetes. Rates of pre-eclampsia (12.7%), Cesarean section (44.3%) and maternal mortality (0.6%) found among women with type 1 diabetes are considerably higher than in the background population. Hypertension and postpartum hemorrhage are more likely to be found in pregnancies complicated by diabetes. Pregnant women with type 1 diabetes present a death rate 109 times greater than the general population and 3.4 times greater than in nonpregnant type 1 diabetic women. (Carlos Antonio Negrato et al, 2012).

2.2.4 Common Symptoms of Diabetes:

Hunger and fatigue: body converts the food into glucose that cells use for energy. But y cells need insulin to bring the glucose in. If body doesn't make enough or any insulin, or if cells resist the insulin, the glucose can't get into them and they have no energy. This can make patient more hungry and tired than usual. (Colin Tidy et al, 2016)

Peeing more often and being thirstier: the average person usually has to pee between four and seven times in 24 hours, but people with diabetes may go a lot more. Normally body reabsorbs glucose as it passes through kidneys. But when diabetes pushes blood sugar up, body may not be able to bring it all back in. It will try to get rid of the extra by making more urine, and that takes fluids. So, it has to go more often, and might pee out more, too. Because peeing so much, patient can get very thirsty. When patient drink more, also pees more. (Colin Tidy et al, 2016)

Dry mouth and itchy skin**:** because body is using fluids to make pee, there's less moisture for other things. Patient could get dehydrated, and patient may feel dry mouth. Dry skin can make patient itchy.

Blurred vision: Changing fluid levels in your body could make the lenses in your eyes swell up. They change shape and lose their ability to focus. (Colin Tidy et al,

2.3 Embryology:

From a single cell to a baby in 9 months a developmental process that represents an amazing integration of increasingly complex phenomena. The study of these phenomena is called embryology, and the field includes investigations of the molecular, cellular, and structural factors contributing to the formation of an organism. The first 8 weeks of human development is called the period of embryogenesis or organogenesis, the period from that point on until birth is called the fetal period, a time when differentiation continues while the fetus grows and gains weight. A normal pregnancy lasts for 9 months, 40 weeks, or 280 days. However, it may last up to 42 weeks. As a result, typically the first trimester is defined as weeks 1 through 12, the second trimester is defined as weeks 13 through 26, and the third trimester is defined as weeks 27 through 42. Fetal age is determined by the last menstrual period, which may be referred to as menstrual age or gestational age. (T.W Sadler et al, 2012).

2.3.1Gametes Formation:

2.3.1.1 Spermatogenesis:

Time period: puberty to death.

In males, meiosis occurs during spermatogenesis, in which spermatogonia in the testes become spermatozoa. The germ cells that will form the male gametes (spermatozoa) are derived from germ cells that migrate from the yolk sac into the site of early gonad formation. (Samuel Webster et al, 2016)

Aims of spermatogenesis: Spermatogonia are diploid germ cells in the testes that maintain their numbers by mitosis, thus maintaining spermatozoa numbers through life. Spermatogonia contain both X and Y sex chromosomes. At a certain point a spermatogonium will stop its other duties and begin meiosis. The cells that result will then pass through more stages of maturation and development and will become mature spermatozoa capable of travelling to and fertilizing an ovum. (Samuel Webster et al, 2016)

Anatomy: The testis is made up of very long, tightly coiled tubes called the seminiferous tubules that are surrounded by layers of connective tissue, blood vessels and nerves. The seminiferous tubules are linked to straight tubules and a network of tubes called the rete testis which lead to the epididymis. The epididymis is another collection of tubes on the posterior edge of the testes that passes inferiorly and is continuous with the ductus deferens (also known as the vas deferens). The ductus deferens carries mature spermatozoa from the testis to the urethra. Spermatogonia are found in the walls of the seminiferous tubules, and as they progress through spermatogenesis they pass towards the Lumina of those tubules. Ley dig cells within the testes produce testosterone. Sertoli cells are also found in the seminiferous tubules, and produce a number of hormones. (Samuel Webster et al, 2016)

Spermatocytogenesis: The spermatogonia that we begin the process with are called spermatogonia A cell. These are the stem cells that proliferate and replenish the root source of all spermatozoa. The cells that are about to begin meiosis are called spermatogonia B cells, and can be recognized partly because they are

connected to one another by cytoplasmic bridges. They continue to divide by mitosis until they become primary spermatocytes. The cytoplasmic bridges will maintain connections between a group of cells during spermatogenesis, synchronizing the process and batch producing groups of spermatozoa. The primary spermatocytes enter meiosis I. Homologous recombination of chromosomes occurs in this stage. One primary spermatocyte becomes two secondary spermatocytes. These cells are now haploid. Each secondary spermatocyte may contain an X or a Y sex chromosome. Secondary spermatocytes enter meiosis II and again divide, forming spermatids. As the DNA was not replicated in meiosis II these cells have half their original DNA. During fertilization this DNA will be combined with the DNA of the maternal ovum. This is the end of the first stage of spermatogenesis, known as spermatocytogenesis (Samuel Webster et al, 2016)

Spermiogenesis: During spermiogenesis the rounded spermatid cell changes shape, becoming elongated and developing the familiar head and tail. The cell loses cytoplasm, the nucleus is packed into the head, mitochondria become concentrated in the first part of the tail and an acrosome forms around the tip of the head. The acrosome contains enzymes that will help the sperm penetrate the outer layers of the ovum during fertilization. At the end of spermiogenesis the spermatids have become spermatozoa**.** (Samuel Webster et al, 2016)

Spermatozoa: Spermatogenesis takes around 64 days to produce spermatozoa from germ cells in the above processes. The spermatozoa are then passed in an inactive state to the epididymis, where they continue to mature. During the next week they descend within the epididymis and become motile and ready to be passed into the ductus deferens during ejaculation. (Samuel Webster et al, 2016)

2.3.1.2 Oocyte formation: At puberty, the female begins to undergo regular monthly cycle which controlled by gonadotropin releasing hormone (GRH) which produced by the hypothalamus. These hormones, follicular-stimulating hormone (FSH) and luteinizing hormone (LH) simulate and control changes in ovary. At the beginning of each ovarian cycle, 15 to 20 primary stage (preantral) follicle are

simulated to grow under influence of FSH. Under normal condition, only one oocyte is discharge, the others degenerate and become atretic. FSH also simulates maturation of follicular (granulosa) cell surrounding the oocytes. The granulos a cell with theca interna cells produces estrogens, theca interna cells produce andorotenedione and testosterone, and granular cell convert these hormones to estrone and 17 Beta-estradiol. As result of this estrogen production: the uterine endometrium enters the follicular or proliferative phase, thinning of the cervical mucus occurs to allow passage of sperm; and the anterior lob of pituitary gland is stimulated to secret LH. At mid cycle LH action is to elevate concentration of maturation- promoting factor, causing oocyte to complete meiosis 1 and initiate meiosis 2, stimulates production of progesterone by follicular stromal cells (luteinization), and causes follicular rupture and ovulation. (Bruce M. Carlson, 2014)

Ovulation: In the days immediately preceding ovulation, under the influence of FSH and LH, the vesicular follicle grows rapidly to a diameter of 25mm to become a mature vesicular (grafian) follicle. Coincident with final development of the vesicular follicle, there is an abrupt increase in LH that causes the primary oocyte to complete meiosis I and the follicle to enter the preovulatory mature vesicular stage. Meiosis II is also initiated, but the oocyte is arrested in metaphase approximately 3 hours before ovulation. In the meantime, the surface of the ovary begins to bulge locally, and at the apex, an avascular spot, the stigma, appears. The high concentration of LH increases collagenase activity, resulting in digestion of collagen fibers surrounding the follicle. Prostaglandin levels also increase in response to the surge and cause local muscular contractions in the ovarian wall. Those contractions extrude the oocyte, which together with its surrounding granulosa cells from the region of the cumulus oophorus breaks free (ovulation) and floats out of the ovary. (Bruce M. Carlson, 2014)

Figure (2. 2) The ovulation. (Williams Obstetrics, Cunningham et al, 21ed., McGraw- Hill, 1997)

2.3.2 Oogenesis: Oogenesis begins with fertilization, the process by which the male gamete, the sperm, and female gamete, the oocyte, unit to give rise to a zygote. (T.W Sadler et al, 2012)

2.3.2.1 Fertilization: Fertilization, the process by which male and female gametes fuse, occurs in the ampullary region of the uterine tube. Spermatozoa may remain viable in the female reproductive tract for several days. Only 1% of sperm deposited in the vagina enter the cervix, where they may survive for many hours. This trip from cervix to oviduct can occur as rapidly as 30 minutes or as slow as 6 days. After reaching the isthmus, sperm become less motile and cease their migration. At ovulation, sperm again become motile, perhaps because of chemoattractants produced by cumulus cells surrounding the egg, and swim to the ampulla, where fertilization usually occurs. Spermatozoa are not able to fertilize the oocyte immediately upon arrival in the female genital tract but must undergo capacitation, and the acrosome reaction to acquire this capability. (Kevin Coward et al, 2013)

2.3.2.1.1 Capacitation: Is a period of conditioning in the female reproductive tract that in the human lasts approximately **7** hours. Thus, speeding to the ampulla is not an advantage, since capacitation has not yet occurred and such sperm are not capable of fertilizing the egg. Much of this conditioning during capacitation occurs in the uterine tube and involves epithelial interactions between the sperm and the

mucosal surface of the tube. During this time, a glycoprotein coat and seminal plasma proteins are removed from the plasma membrane that overlies the acrosomal region of the spermatozoa. Only capacitated sperm can pass through the corona cells and undergo the acrosome reaction. The acrosome reaction, which occurs after binding to the zona pellucida, is induced by zona proteins. This reaction culminates in the release of enzymes needed to penetrate the zona pellucida, including acrosin- and trypsin-like substances. (Kevin Coward et al, 2013)

2.3.2.1.2 The Phases of Fertilization Include: Phase 1, penetration of the corona radiates, phase 2, penetration of the zona pellucida, phase 3, fusion of the oocyte and sperm cell membranes. (Kevin Coward et al, 2013)

Phase1 Penetration of the Corona Radiata: Of the 200 to 300 million spermatozoa normally deposited in the female genital tract, only 300 to 500 reach the site of fertilization. Only one of these fertilizes the egg. It is thought that the others aid the fertilizing sperm in penetrating the barriers protecting the female gamete. Capacitated sperm pass freely through corona cells. (Kevin Coward et al, 2013)

Phase2 Penetration of the Zona Pellucida: The zona is a glycoprotein shell surrounding the egg that facilitates and maintains sperm binding and induces the acrosome reaction. Both binding and the acrosome reaction are mediated by the ligand ZP3, a zona protein. Release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona, there by coming in contact with the plasma membrane of the oocyte. Permeability of the zona pellucida changes when the head of the sperm comes in contact with the oocyte surface. This contact results in release of lysosomal enzymes from cortical granules lining the plasma membrane of the oocyte. In turn, these enzymes alter properties of the zona pellucida (zona reaction) to prevent sperm penetration and inactivate species-specific receptor sites for spermatozoa on the zona surface. Other spermatozoa have been found embedded in the zona pellucida, but only one seems to be able to penetrate the oocyte. (Kevin Coward et al, 2013).

Phase 3 Fusion of the Oocyte & Sperm Cell Membranes: The initial adhesion of sperm to the oocyte is mediated in part by the interaction of integrins on the oocyte and their ligands, disintegrins, on sperm. After adhesion, the plasma membranes of the sperm and egg fuse Because the plasma membrane covering the acrosomal head cap disappears during the acrosome reaction, actual fusion is accomplished between the oocyte membrane and the membrane that covers the posterior region of the sperm head. In the human, both the head and the tail of the spermatozoon enter the cytoplasm of the oocyte, but the plasma membrane is left behind on the oocyte surface. (Kevin Coward et al, 2013).

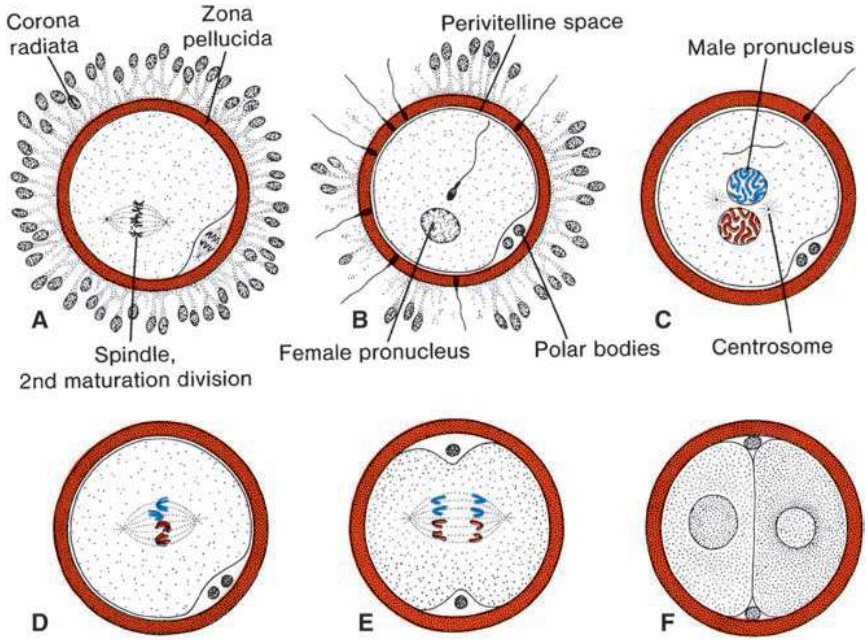


Figure (2.3) A. Oocyte immediately after ovulation, showing the spindle of the second meiotic division. B. A spermatozoon (T. W. Sadler et al, 2012).

When the sperm has penetrated the oocyte, which has finished its second meiotic division, the chromosomes of the oocyte are arranged in a vesicular nucleus, and the female pronucleus. Heads of several sperm are stuck in the zona pellucida. C.

Male and female pronuclei. D, E. Chromosomes become arranged on the spindle, split longitudinally, and move to opposite poles. (Kevin Coward et al, 2013)

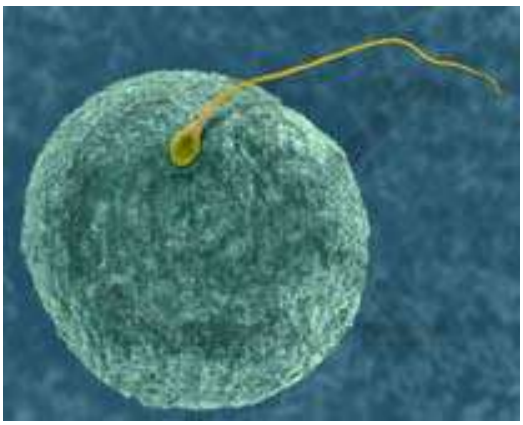


Figure (2.4) The goal - Fertilization (Williams Gynecology, Schorge et al, McGraw- Hill Medical, 2008)

As soon as the spermatozoa has entered the oocyte, the egg responses in three ways:

Cortica & zona reaction: as a result of release of cortical oocyte granules, which contain lysosomal enzymes, the oocyte membrane becomes impenetrable to other spermatozoa, and the zona pellucida alters its structure and composition to prevent sperm binding and penetration. (T.W Sadler et al, 2012)

Resumption of second meiotic division: The oocyte finishes its second meiotic division immediately after entry of the second polar body and the other is the definitive oocyte. It's chromosomes (22 plus X) arrange themselves in a vesicular nucleus known as female pronucleus. (T.W Sadler et al, 2012)

Metabolic activation of the egg: The activating factor is probably carried by spermatozoon. Activation encompasses the initial cellular and molecular event associated with early embryogenesis. At this time spermatozoa becomes swollen and form the male pronucleus and lies close the female pronucleus. The tail detaches and degenerate. During growth of male and female pronuclei, each one must replicate its DNA, if not, each cell of the tow cell zygote has only the half of the normal amount of the DNA. Immediately after DNA synthesis, chromosomes organize on the spindle in preparation for normal mitotic division. The 23 maternal

and 23 paternal (double) chromosomes split longitudinally at the centromere, and sister chromatids move to opposite poles, providing each cell of the zygote with normal diploid number of chromosomes and DNA. As sister chromatids and opposite poles, a deep furrow appears on the surface of the cell, gradually dividing the cytoplasm into two parts. (T.W Sadler et al, 2012)

2.3.2.1. The Main Results of Fertilization are as Follows:

Restoration of the diploid number of chromosomes, half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents. **(**Samuel Webster et al, 2016)

Determination of the sex of the new individual: An X-carrying sperm produces a female (XX) embryo, and a Y-carrying sperm produces a male (XY) embryo. Therefore, the chromosomal sex of the embryo is determined at fertilization. **(**Samuel Webster et al, 2016)

Initiation of cleavage: without fertilization, the oocyte usually degenerates 24 hours after ovulation. Cleavage, occur when the zygote has reached the two-cell stage, it then undergoes a series of mitotic divisions, increasing the numbers of cells. These cells, which become smaller with each cleavage division, are known as blastomeres. **(**Samuel Webster et al, 2016)

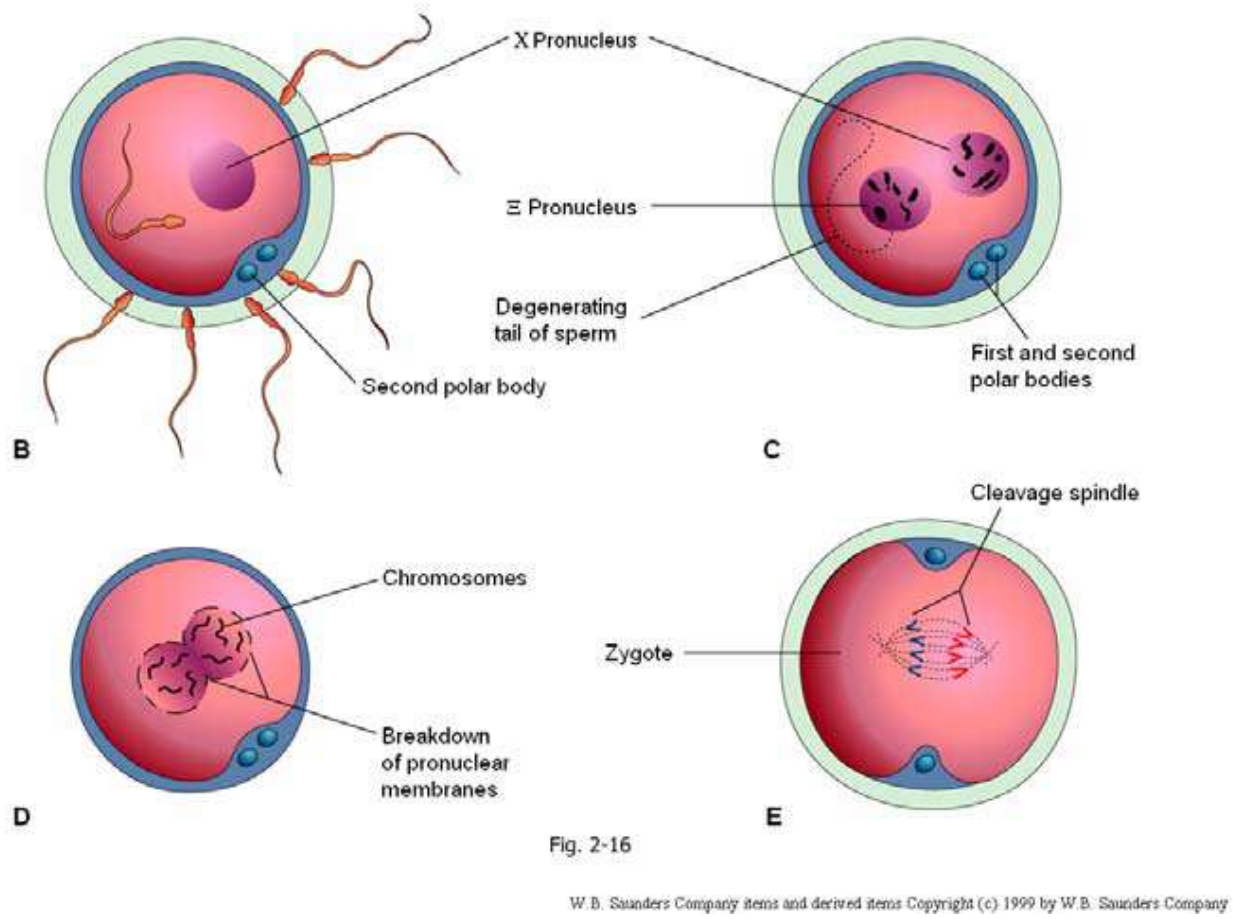


Figure (2.5) Pronuclei Development, Fusion and Formation of First Mitotic Division Figure (Williams Gynecology, Schorge et al, McGraw- Hill Medical, 2008)

Until the eight-cell stage, they form a loosely arranged clump. After the third cleavage, however, blastomeres maximize their contact with each other, forming a compact ball of cells held together by tight junctions. This process, compaction, segregates inner cells, which communicate extensively by gap junctions, from outer cells. Approximately 3 days after fertilization, cells of the compacted embryo divide again to form a 16-cell morula (mulberry). Inner cells of the morula constitute the inner cell mass, and surrounding cells compose the outer cell mass. The inner cell mass gives rise to tissues of the embryo proper, and the outer cell mass forms the trophoblast, which later contributes to the placenta. (T. W Sadler et al, 2012).

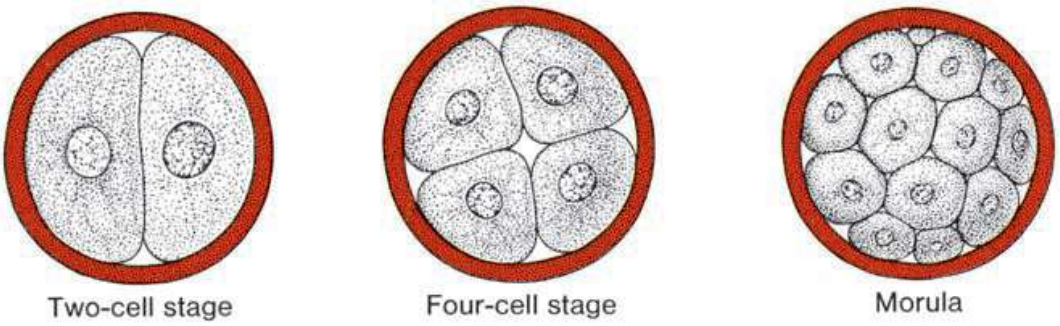


Figure (2.6) Development of the zygote from the two-cell stage to the late morula stage. (T. W. Sadler et al, 2012)

2.3.2.2 Blastocyst Formation: About the time the morula enters the uterine cavity, fluid begins to penetrate through the zona pellucida into the intercellular spaces of the inner cell mass. Gradually, the intercellular spaces become confluent, and finally, a single cavity, the blastocele forms. At this time, the embryo is a blastocyst. Cells of the inner cell mass, now called the embryoblast, are at one pole, and those of the outer cell mass, or trophoblast, flatten and form the epithelial wall of the blastocyst. The zona pellucida has disappeared, allowing implantation to begin. In the human, trophoblastic cells over the embryoblast pole begin to penetrate between the epithelial cells of the uterine mucosa on about the sixth day. New studies suggest that L selectin on trophoblast cells and its carbohydrate receptors on the uterine epithelium mediate initial attachment of the blastocyst to the uterus. Selectins are carbohydrate-binding proteins involved in interactions between leukocytes and endothelial cells that allow leukocyte "capture" from flowing blood. A similar mechanism is now proposed for "capture" of the blastocyst from the uterine cavity by the uterine epithelium. Following capture by selectins, further attachment and invasion by the trophoblast involve integrins, expressed by the trophoblast and the extracellular matrix molecules laminin and fibronectin. Integrin receptors for laminin promote attachment, while those for fibronectin stimulate migration. These molecules also interact along signal transduction pathways to regulate trophoblast differentiation, so that implantation is the result of mutual trophoblastic and endometrial action. Hence, by the end of the first week of development, the human zygote has passed through the morula

and blastocyte stages and has begun implantation in the uterine mucosa. **(**Samuel Webster et al, 2016)

2.3.2.3 Uterus at Time of Implantation: The wall of uterus is consisting of three layers: endometrium or mucosa lining the inside wall, myometrium which is thick layer of smooth muscle, premetrium which is peritoneal covering lining the outside wall. During menstrual cycle, the uterine endometrium passes through three stages, the: follicular or proliferative phase, secretory or progestational phase, menstrual phase. The proliferative phase begins at the end of the menstrual phase, is under the influence of estrogen, and parallels growth of the ovarian follicles. The secretory phase begins approximately 2 to 3 days after ovulation in response to progesterone produced by the corpus luteum. If fertilization does not occur, shedding of the endometrium (compact and spongy layers) marks the beginning of the menstrual phase. If fertilization does occur, the endometrium assists in implantation and contributes to formation of the placenta. Later in gestation, the placenta assumes the role of hormone production, and the corpus luteum degenerates. At the time of implantation, the mucosa of the uterus is in the secretory phase, during which time uterine glands and arteries become coiled and the tissue becomes succulent. As a result, three distinct layers can be recognized in the endometrium: a superficial compact layer, an intermediate spongy layer, and a thin basal layer. Normally, the human blastocyst implants in the endometrium along the anterior or posterior wall of the body of the uterus, where it becomes embedded between the openings of the glands. If the oocyte is not fertilized, venules and sinusoidal spaces gradually become packed with blood cells, and an extensive diapedesis of blood into the tissue is seen. When the menstrual phase begins, blood escapes from superficial arteries, and small pieces of stroma and glands break away. During the following 3 or 4 days, the compact and spongy layers are expelled from the uterus, and the basal layer is the only part of the endometrium that is retained. This layer, which is supplied by its own arteries, the basal arteries, functions as the regenerative layer in the rebuilding of glands and arteries in the proliferative phase. (T.W. Sadler et al, 2012).

Chorion and Placenta: Primary chorionic villi develop between 13 and 15 days after ovulation (end of 4th week of gestation). Simultaneously, blood vessels start to develop in the extra-embryonic mesoderm of the yolk sac, the connecting stalk and the chorion. The primary villi are composed of a central mass of cytotrophoblast surrounded by a thick layer of syncytiotrophoblast. During the 5th week of gestation, they acquire a central mesenchymal core from the extra-embryonic mesoderm and become branched, forming the secondary villi. The appearance of embryonic blood vessels within their mesenchymal cores transforms the secondary villi into tertiary villi. Up to 10 weeks' gestation, which corresponds to the last week of the embryonic period (stages 19 to 23), villi cover the entire surface of the chorionic sac. As the gestational sac grows during fetal life, the villi associated with the decidua capsularis surrounding the amniotic sac become compressed and degenerate, forming an avascular shell known as the chorion leave, or smooth chorion. Conversely, the villi associated with the decidua basalis proliferate, forming the chorion frondosum or definitive placenta. (Ash Monga et al, 2011)

Normal Placentation: As soon as the blastocyst has hatched, the trophoectoderm layer attaches to the cell surface of the endometrium and, by simple displacement, early trophoblastic penetration within the endometrial stroma occurs. Progressively, the entire blastocyst will sink into maternal decidua and the migrating trophoblastic cells will encounter venous channels of increasing size, then superficial arterioles and, during the 4th week, the spiral arteries. The trophoblastic cells infiltrate deep into the decidua and reach the deciduo-myometrial junction at between 8- and 12-weeks' gestation. This extravillous trophoblast penetrates the inner third of the myometrium via the interstitial ground substance and affects its mechanical and electrophysiological properties by increasing its expansile capacity. The trophoblastic infiltration of the myometrium is progressive and achieved before 18 weeks' gestation in normal pregnancies (Ash Monga et al, 2011).

2.3.2.4 First to Six Week: A mature ovum is released through ovulation at around day 14 of the menstrual cycle, as the Grafian follicle ruptures and liberates the ovum into the peritoneal cavity. The fimbria of the fallopian tube transports the ovum into the distal portion of the tube, the infundibulum. Conception, also referred to as fertilization, is the union of an ovum with a sperm. A sperm, which can live up to 72 hours, unites with the egg in the distal one third of the fallopian tube, most likely in the ampulla. Conception usually occurs within 24 hours after ovulation. The combination of the sperm and ovum produces a structure referred to as the zygote. The zygote undergoes rapid cellular division and eventually forms into a cluster of cells called the morula. The morula continues to differentiate and form a structure referred to as the blastocyst. The outer tissue layer of the blastocyst is comprised of syncytiotrophoblastic tissue, also referred to as trophoblastic cells. The inner part of the blastocyst will develop into the embryo, amnion, umbilical cord, and the primary and secondary yolk sacs. The outer part, the trophoblastic tissue, will develop into the placenta and chorion. On days 20 or 21 of the menstrual cycle, the blastocyst begins to implant into the decidualized endometrium at the level of the uterine fundus. By 28 days, complete implantation has occurred and all early connections have been established between the gestation and the mother. The blastocyst makes these links with the maternal endometrium via small projections of tissue called chorionic villi. The implantation of the blastocyst within the endometrium may cause some women to experience a small amount of vaginal bleeding. This is referred to as implantation bleeding. (Steven. M. Penny, 2011).

The fourth week of gestation is an extremely dynamic stage in the pregnancy. The primary yolk sac regresses during week 4 and two separate membranes are formed. The outer membrane is the chorionic sac or gestational sac. Within the gestational sac is the amnion or amniotic sac. By the end of week 4, the secondary yolk sac becomes wedged between these two membranes in an area called the chorionic cavity or extraembryonic coelom. The developing embryo is located between the yolk sac and amnion at 4 weeks. At this time, the alimentary canal is formed. It

will become the foregut, midgut, and hindgut. The neural tube also begins to develop at this time. The neural tube will become the fetal head and spine. By 5 weeks, suspicion of pregnancy abounds, as the woman misses the scheduled onset of menses for the month. Within the developing gestation, the embryonic heart begins to beat for the first time. By 6 weeks, all internal and external structures are in the process of forming. (Steven. M. Penny, 2011)

2.3.2.5 Embryo Ninth to 12 weeks: Physiologic bowel herniation begins at 8 weeks, which marks the developmental stage when the midgut migrates into the base of the umbilical cord. This phenomenon is developmentally normal. The sonographer should determine the gestational age based on crown rump length and greater than 3 mm between 11 and 14 weeks is considered abnormal and warrants a follow-up examination and fetal karyotyping. The guidelines for obtaining the NT measurement have been established by the American Institute of Ultrasound in Medicine and can be found at www.aium.org. They understand that physiologic herniation is normal during this early stage of maturity. Conversely, if physiologic bowel herniation does not resolve by 12 weeks, a follow-up examination is often warranted.4 With the end of the first trimester, the fetal limbs are much more readily identifiable with sonography. Inside the fetal head, the lateral ventricles may be noted, containing the echogenic choroid plexus. The cerebral hemispheres can also be separated by the echogenic, linear falx cerebri, which lies within the midline of the brain. Fetal movement, the stomach, urinary bladder, umbilical cord, and spine can also be noted by the end of the first trimester. However, a detailed examination of this anatomy is usually not performed at this time. (Steven. M. Penny, 2011).

2.3.2.6 Nuchal Translucency (11 to 14 weeks): The evaluation of the nuchal translucency has become a vital part of early first-trimester screening. This translucency is represented by a thin membrane along the posterior aspect of the fetal neck, which can be measured sonographically. The most common abnormalities associated with increased fetal nuchal translucency are trisomy 21, trisomy 18, Turner syndrome, and congestive heart failure. The measurement of

this area is performed in the sagittal plane to the fetus, with the fetus in a neutral position. The nuchal translucency is optimally measured between 11- and 14-weeks' gestation, when the crown rump length measures between 45- and 85-mm. Care should be taken as to not confuse the amnion for a prominent nuchal translucency, as the fetus may be resting on the amnion. The normal range of thickness of nuchal translucency is based on the gestational age, although most often a measurement greater than 3 mm between 11 and 14 weeks is considered abnormal and warrants a follow-up examination and fetal karyotyping. The guidelines for obtaining the NT measurement have been established by the American Institute of Ultrasound in Medicine. They understand that physiologic herniation is normal during this early stage of maturity. Conversely, if physiologic bowel herniation does not resolve by 12 weeks, a follow-up examination is often warranted. With the end of the first trimester, the fetal limbs are much more readily identifiable with sonography. Inside the fetal head, the lateral ventricles may be noted, containing the echogenic choroid plexus. The cerebral hemispheres can also be separated by the echogenic, linear falx cerebri, which lies within the midline of the brain. Fetal movement, the stomach, urinary bladder, umbilical cord, and spine can also be noted by the end of the first trimester. However, a detailed examination of this anatomy is usually not performed at this time. (Steven. M. Penny, 2011).

2.3.2.7 Third to Eighth Weeks (The Embryonic Period): The embryonic period, occurs from the third to the eighth weeks of development and is the time when each of the three germ layers, ectoderm, mesoderm, and endoderm, gives rise to a number of specific tissues and organs. By the end of the embryonic period, the main organ systems have been established, rendering the major features of the external body form recognizable by the end of the second month. (Samuel Webster et al, 2016).

2.3.2.7.1 Derivation of The Ectodermal Germ Cell: At the beginning of the third week, the ectodermal germ layer has the shape of a disc that is broader in the cephalic than in the caudal region Appearance of the notochord and prechordal

mesoderm induces the overlying ectoderm to thicken and form the neural plate. Cells of the plate make up the neuroectoderm, and their induction represents the initial event in the process of neurolation. (Bruce M. Carlson 2014).

2.3.2.7.2 Neurolation: Neurolation is the process whereby the neural plate forms the neural tube. By the end of the third week, the lateral edges of the neural plate become elevated to form neural folds, and the depressed mid region forms the neural groove. Gradually, the neural folds approach each other in the midline, where they fuse. Fusion begins in the cervical region (fifth somite) and proceeds cranially and caudally. As a result, the neural tube is formed. Until fusion is complete, the cephalic and caudal ends of the neural tube communicate with the amniotic cavity by way of the anterior (cranial) and posterior (caudal) neuropores, respectively. Closure of the cranial neuropore occurs at approximately day 25 (18 to 20 somite stage), whereas the posterior neuropore closes at day 28 (25 somite stage). Neurolation is then complete, and the central nervous system is represented by a closed tubular structure with a narrow caudal portion, the spinal cord, and a much broader cephalic portion characterized by a number of dilations, the brain vesicles. By the time the neural tube is closed, two bilateral ectodermal thickenings, the otic placodes and the lens placodes, become visible in the cephalic region of the embryo. During further development, the otic placodes invaginate and form the otic vesicles, which will develop into structures needed for hearing and maintenance of equilibrium. At approximately the same time, the lens placodes appear. These placodes also invaginate and, during the fifth week, form the lenses of the eyes. In general, the ectodermal germ layer gives rise to organs and structures that maintain contact with the outside world central nervous system, peripheral nervous system, sensory epithelium of the ear, nose, and eye, and epidermis, including the hair and nails. In addition, it gives rise to subcutaneous glands, mammary glands, pituitary gland, and enamel of the teeth. (Samuel Webster et al, 2016).

2.3.2.7.3 Derivative of The Mesodermal Germ Cell: Cell of the mesodermal germ layer form a thin sheet of loosely woven tissue on each side of the midline.

By approximately the 17th day, cells close to midline proliferate and form a thickened plate of tissue known as proximal mesoderm. More laterally, the mesoderm layer remains thin and is known as lateral plate. With appearance and coalescence of intercellular cavities in the lateral plate, this tissue is divided into two layers a layer continuous with mesoderm covering the amnion, known as somatic or parietal mesoderm layer, and a layer continuous with mesoderm covering the yolk sac, known as the splanchnic. Together, these layers line a newly formed cavity, the intra embryonic cavity, which is continuous with extra embryonic cavity on each side of embryo. Intermediate mesoderm connects paraxial and lateral plate mesoderm. (Bruce M. Carlson, 2014)

2.3.2.7.3.1Paraxial Mesoderm: By the beginning of the third week, paraxial mesoderm begins to be organized into segment. These segments, known as somitomeres, first appear in cephalic region of embryo, and their formation proceeds cephalocaudally. In the head region, somitomeres form in association with segmentation of the neural plate into neuromeres and contribute to mesenchyme in the head. From the occipital region caudally, somitomeres further organize into somites. The first pair of somites arises in the occipital region of the embryo at approximately the 20th day of development. From here, new somites appear in craniocaudal sequence at a rate of approximately three pairs per day until, at the end of the fifth week, 42 to 44 pairs are present. There are 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 8 to 10 coccygeal pairs. The first occipital and the last five to seven coccygeal somites later disappear, while the remaining somites form the axial skeleton. (Bruce M. Carlson 2014)

2.3.2.7.3.2 Intermediate Mesoderm: Intermediate mesoderm, which temporarily connects paraxial mesoderm with the lateral plate, differentiates into urogenital structures. In cervical and upper thoracic regions, it forms segmental cell clusters (future nephrotomes), whereas more caudally, it forms an unsegmented mass of tissue, the nephrogenic cord. Excretory units of the urinary system and the gonads develop from this partly segmented, partly unsegmented intermediate mesoderm. (Bruce M. Carlson 2014)

2.3.2.7.3.3 Lateral Plate Mesoderm: Lateral plate mesoderm splits into parietal (somatic) and visceral (splanchnic) layers, which line the intra embryonic cavity and surround the organs, respectively. Mesoderm from the parietal layer, together with overlying ectoderm, forms the lateral body wall folds. These folds, together with the head (cephalic), and tail (caudal folds) close the ventral body wall. The parietal layer of lateral plate mesoderm then forms the dermis of the skin in the body wall and limbs, the bones and connective tissue of the limbs, and the sternum. In addition, sclerotome and muscle precursor cells that migrate into the parietal layer of lateral plate mesoderm form the costal cartilages, limb muscles, and most of the body wall muscles. The visceral layer of lateral plate mesoderm, together with embryonic endoderm, forms the wall of the gut tube. Mesoderm cells of the parietal layer surrounding the intra embryonic cavity form thin membranes, the mesothelial membranes, or serous membranes, which will line the peritoneal, pleural, and pericardial cavities and secrete serous fluid Mesoderm cells of the visceral layer form a thin serous membrane around each organ.(Bruce M. Carlson 2014)

Figure (2.7) Dorsal view of somites forming along the neural tube (the ectoderm has been partially removed). Somites form from unsegmented presomitic paraxial mesoderm caudally and become segmented in more cranially positioned regions. (W.T Sadler et al,2012).

2.3.2.7.4 Blood and Blood Vessels: Blood cells and blood vessels also arise from mesoderm. Blood vessels form in two ways: vasculogenesis, whereby vessels arise from blood islands and angiogenesis, which entails sprouting from existing vessels. The first blood islands appear in mesoderm surrounding the wall of the yolk sac at 3ed week and later in lateral plate mesoderm and other regions. These

islands arise from mesoderm cells that are induced to form hemangioblasts, a common precursor for vessel and blood cell formation. Although the first blood cells arise in blood islands in the wall of the yolk sac, this population is transitory. The definitive hematopoietic stem cells are derived from mesoderm surrounding the aorta in a site near the developing mesonephric kidney called the aorta gonad-m esonephros region. These cells colonize the liver, which becomes the major hematopoietic organ of the embryo and fetus from approximately the second to seventh months of development. Stem cells from the liver colonize the bone marrow, the definitive blood-forming tissue, in the seventh month of gestation, and thereafter, the liver loses its blood-forming function. (Samuel Webster et al, 2016).

2.3.2.7.5 Derivative of The Endodermal Germ Layer: The gastrointestinal tract is the main organ system derived from the endodermal germ layer. This germ layer covers the ventral surface of the embryo and forms the roof of the yolk sac. With development and growth of the brain vesicles, the embryonic disc begins to bulge into the amniotic cavity. Lengthening of the neural tube now causes the embryo to curve into the fetal position as the head and tail regions (folds) move ventrally. Simultaneously, two lateral body wall folds form and also move ventrally to close the ventral body wall. As the head and tail and two lateral folds move ventrally, they pull the amnion down with them, so embryo lies within the amniotic cavity. The ventral body wall closes completely except for the umbilical region where the connecting stalk and yolk sac duct remain attached. As a result of cephalocaudal growth and closure of the lateral body wall folds a continuously larger portion of the endodermal germ layer is incorporated into the body of the embryo to form the gut tube. The tube is divided into three regions: the foregut, midgut, and hindgut. The midgut communicates with the yolk sac by way of a broad stalk, the vitelline (yolk sac) duct. The cephalic end of the foregut is temporarily bounded by an ectodermal–endodermal membrane called the oropharyngeal membrane. This membrane separates the stomadeum, the primitive oral cavity derived from ectoderm, from the pharynx, a part of the foregut derived from endoderm. In the

fourth week, the oropharyngeal membrane ruptures, establishing an open connection between the oral cavity and the primitive gut. The hindgut also terminates temporarily at an ectodermal–endodermal membrane, the cloacal membrane. This membrane separates the upper part of the anal canal, derived from endoderm, from the lower part, called the proctodeum, which is formed by an invaginating pit lined by ectoderm. The membrane breaks down in the seventh week to create the opening for the anus. Another important result of cephalocaudal growth and lateral folding is partial incorporation of the allantois into the body of the embryo, where it forms the cloaca. Hence, the endodermal germ layer initially forms the epithelial lining of the primitive gut and the intraembryonic portions of the allantois and vitelline duct. During further development, endoderm gives rise to: epithelial lining of the respiratory tract, parenchyma of the thyroid, parathyroids, liver, and pancreas, reticular stroma of the tonsils and the thymus, epithelial lining of the urinary bladder and the urethra, epithelial lining of the tympanic cavity and auditory tube. (Bruce M. Carlson 2014)

2.3.2.7.6 External Appearance During the Second Month: At the end of the fourth week, when the embryo has approximately 28 somites, the main external features are the somites and pharyngeal arches. The age of the embryo is therefore usually expressed in somites. Because counting somites becomes difficult during the second month of development, the age of the embryo is then indicated as the crown rump length (CRL) and expressed in millimeters. CRL is measured from the vertex of the skull to the midpoint between the apices of the buttocks. (T.W Sadler et al, 2012).

Table (2.2): CRL in mm and approximate age of embryo in weeks: (T.W Sadler et al, 2012)

CRL in mm	Approximately Age in Weeks
5---8	5
10--14	6
17--22	7
28--30	8

2.3.2.8 Formation of The Diaphragm: The diaphragm consists of components of the septum transversum, pleuroperitoneal folds, some esophageal mesentery and a little muscular ingrowth from the dorsal and lateral body walls. The septum transversum originates around day 22 at a cervical level, but caudal to the developing heart. It receives innervation from spinal nerves C3–C5, the beginning of the phrenic nerve. With growth of the embryo the position alters to rest at the level of the thoracic vertebrae. The septum transversum is a boundary between the abdominal cavity and the thoracic cavity. There are two connections between these cavities the pericardioperitoneal canals. The pleuroperitoneal folds arise from the dorsal body wall and eventually close off the pericardioperitoneal canals and prevent communication between the abdominal and thoracic cavities. The pleuroperitoneal folds fuse with the septum transversum, the esophageal mesentery and the muscular ingrowth from the body walls to form the diaphragm. Muscle cells from the septum transversum and the body wall invade the folds forming the muscular part of the diaphragm. The septum transversum forms the central tendon and the mesentery of the esophagus merges into the central tendon, thus allowing passage of the aorta, vena cava and esophagus. (Samuel Webster et al, 2016)

2.3.2.9 Third Month to Birth: The period from the beginning of the ninth week to birth is known as the fetal period. It is characterized by maturation of tissues and organs and rapid growth of the body. The length of the fetus is usually indicated as the crown rump length (CRL) (sitting height) or as the crown-heel length (CHL), the measurement from the vertex of the skull to the heel (standing height). These

measurements, expressed in centimeters, are correlated with the age of the fetus in weeks or months Growth in length is particularly striking during the third, fourth, and fifth months, while an increase in weight is most striking during the last **2** months of gestation. (T.W Sadler et al, 2012).

Table (2.3) The fetus development in cm and grams. (T.W Sadler et al, 2012):

Age in Weeks	CRL (cm)	Weight(g)
9-12	5-8	10-45
13-16	9-14	60-200
17-20	15-19	250-450
21-24	20-23	500-820
25-28	24-27	900-1300
29-32	28-30	1400-2100
33-39	31-34	2200-2900
37-38	35-36	3000-3400

2.3.2.9.1 Monthly Changes: One of the most striking changes taking place during fetal life is the relative slowdown in growth of the head compared with the rest of the body. At the beginning of the third month, the head constitutes approximately half of the CRL. By the beginning of the fifth month, the size of the head is about one third of the CHL, and at birth, it is approximately one quarter of the CHL. Hence, over time, growth of the body accelerates but that of the head slows down. During the third month, the face becomes more human looking. The eyes, initially directed laterally, move to the ventral aspect of the face, and the ears come to lie close to their definitive position at the side of the head. The limbs reach their relative length in comparison with the rest of the body, although the lower limbs are still a little shorter and less well developed than the upper extremities. Primary ossification centers are present in the long bones and skull by the 12th week. Also, by the 12th week, external genitalia develop to such a degree that the sex of the fetus can be determined by external examination (ultrasound). During the sixth

week, intestinal loops cause a large swelling (herniation) in the umbilical cord, but by the 12th week, the loops have withdrawn into the abdominal cavity. At the end of the third month, reflex activity can be evoked in aborted fetuses, indicating muscular activity. During the fourth and fifth months, the fetus lengthens rapidly and at the end of the first half of intrauterine life, its CRL is approximately 15cm, about half the total length of the newborn. The weight of the fetus increases little during this period and by the end of the fifth month is still <500g. The fetus is covered with fine hair, called lanugo hair, eyebrows and head hair are also visible. During the fifth month, movements of the fetus can be felt by the mother. During the second half of intrauterine life, weight increases considerably, particularly during the last 2.5 months, when 50% of the full-term weight (approximately 3,200g) is added. During the sixth month, the skin of the fetus reddish and has a wrinkled appearance because of the lack of underlying connective tissue. A fetus born early in the sixth month has great difficulty surviving. Although several organ systems are able to function, the respiratory system and the central nervous system have not differentiated sufficiently, and coordination between the two systems is not yet well established. By 6.5 to 7 months, the fetus has a CRL of about 25 cm and weighs approximately 1,100 g. If born at this time, the infant has a 90% chance of surviving. During the last 2 months, the fetus obtains well-rounded contours as the result of deposition of subcutaneous fat. By the end of intrauterine life, the skin is covered by a whitish, fatty substance (vernix caseosa) composed of secretory products from sebaceous glands. At the end of the ninth month, the skull has the largest circumference of all parts of the body, an important fact with regard to its passage through the birth canal. At the time of birth, the weight of a normal fetus is 3,000 to 3,400g, its CRL is about 36 cm, and its CHL is about 50 cm. Sexual characteristics are pronounced, and the testes should be in the scrotum. (T.W Sadler et al, 2012).

2.3.3 Systemic Based Embryology:

2.3.3.1 Cerebral Embryology: By 4.5 weeks the neural plate, the structure that will form the central nervous system, has developed. The neural plate will give rise

to the neural tube, which will become the spine and the brain. Initially, the brain is separated into three primary vesicles termed the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain). These vesicles will continue to develop and form critical brain structures. Sonographically, the rhombencephalon may be noted within the fetal cranium during the first trimester. (Steven. M. Penny, 2011)

2.3.3.2 Normal Fetal Skull & Brain Anatomy: The skull consists of eight cranial bones. These bones are connected by structures known as sutures. Fetal sutures may be noted during a routine sonographic examination as hypoechoic spaces between the bones. Because of the flexibility of sutures, the fetal cranial bones remain slightly mobile until delivery to facilitate the passage of the skull through the birth canal. Premature fusion of the sutures. (Steven. M. Penny, 2011).

2.3.3.3 Head, Neck, Ear, & Eye: The head region of the embryo is formed from the pharyngeal arches that develop in the fourth week from mesenchymal cells derived from the neural crest, lateral plate mesoderm and paraxial regions. There are five pairs of pharyngeal arches that form in a rostrocaudal succession, numbered 1,2,3,4,5 and 6. Arch 5 never develop in humans or degrades quickly. Each arch consists of an ectodermal surface (pharyngeal cleft or grooves), mesenchymal core and endodermal inner surface (pharyngeal pouch and membrane) and contains cartilaginous skeletal elements, striated muscles, a cranial never and aortic artery. Arch 1 form the upper and lower jaw and also participates in face and plate development. Arch 2 form the jaw as well as contribute to the hyoid bone and greater cornu, while arch 4 and 6 fuse to contribute to laryngeal development. The pharyngeal pouches grow as pockets between arches and gives rise largely to components of the ear. The second pouch is mostly concerned with palatine tonsil development. The third pouch contribute to parathyroid and thymus glands, while the fourth also play a part in parathyroid and thyroid development. The fifth pouch becomes fused with prominence, and a pair of maxillary and mandibular prominence, which grow and merge together. A pair of ectodermal placodes develops the frontonasal prominence which also give rise to the nose.

Both parts of the eye and ear are formed from ectodermal placodes. Which is a part of the fourth pouch. The human face is formed between the fourth and ten weeks, by fusion of five facial primodia which includes the frontonasal. (Steven M. Penny, 2011).

2.3.3.4 The Axial Skeleton:

Cranium: The skull can be divided into another two parts: the neurocranium (encasing the brain) and the viscerocranium (of the face).

Neurocranium: The bones at the base of the skull begin to develop from cells originating in the occipital somites (paraxial mesoderm) and neural crest cells that surround the developing brain. These cartilaginous plates fuse and ossify (endochondral ossification) forming the sphenoid, ethmoid and occipital bones and the petrous part of the temporal bone. A membranous part originates from the same source and forms the frontal and parietal bones. These plates ossify into flat bones (through intramembranous ossification) and are connected by connective tissue sutures. Where more than two bones meet in the foetal skull a fontanelle is present. The anterior fontanelle is the most prominent, occurring where the frontal and parietal bones meet. Fontanelles allow considerable movement of the cranial bones, enabling the calvaria (upper cranium) to change shape and pass through the birth canal. (Steven M. Penny, 2011).

Viscerocranium: Cells responsible for the formation of the facial skeleton originate from the pharyngeal arches, and the viscerocranium also has cartilaginous and membranous parts during development. The cartilaginous viscerocranium forms the stapes, malleus and incus bones of the middle ear, and the hyoid bone and laryngeal cartilages. The squamous part of the temporal bone (later part of the neurocranium), the maxilla, mandible and zygomatic bones develop from the membranous viscerocranium. (Steven M. Penny, 2011).

Vertebrae: In week 4, cells of the sclerotome migrate to surround the notochord. Undergoing reorganization, they split into cranial and caudal parts. The cranial half contains loosely packed cells, whereas the caudal cells are tightly condensed.

The caudal section of one sclerotome joins the cranial section of the next sclerotome. This creates vertebrae that are 'out of phase' with the segmental muscles that reach across the intervertebral joint. When these muscles contract they induce movements of the vertebral column. (Steven M. Penny, 2011).

Axial Bones: Ribs also form from the sclerotome; specifically, the proximal ribs from the ventromedial part and the distal ribs from the ventrolateral part. The sternum develops from somatic mesoderm and starts as two separate bands of cartilage that come together and fuse in the midline. (Steven M. Penny, 2011).

Appendicular Bones: Endochondral ossification of the long bones begins at the end of week 7. The primary center of ossification is the diaphysis and by week 12 primary centers of ossification appear in all limb long bones. The beginning of ossification of the long bones marks the end of the embryonic period. Ossification of the diaphysis of most long bones is completed by birth, and secondary centers of ossification appear in the first few years of life within the epiphyses. Between the ossified epiphysis and diaphysis, the cartilaginous growth plate (or epiphyseal plate) remains as a region of continuing endochondral ossification. New bone is laid down here, extending the length of growing bones. At around 20 years after birth the growth plate also ossifies, allowing no further growth and connecting the diaphysis and epiphysis. (Steven. M. Penny, 2011).

2.3.3.5 The Cardiovascular system: It is one of the first systems in the embryo to develop. This is necessary to transport oxygen and nutrients to the cell in the rapid growing embryo because it is no longer possible to do this diffusion. In the middle of the third week of embryonic development, angiogenic clusters start to form in the mesoderm in the rostral end of the embryo. These aggregate to form the blood island consist of the haemoblasts which generate all blood cells and endothelial cell which form the vessel wall. Proliferation and fusion of these blood islands creates a primitive network capillary. The embryo then undergoes a serious of folding event. The rostral end of the embryo folds cranially so the heart ends up in the future thoracic region, while lateral folding brings the cardiac region together in the middle. The endothelial heart tube then fuses to form a single primitive heart

tube with cranial and caudal end. The primitive heart tube is divided into a number of primitive chambers separated by grooves. In a caudal to rostral direction the chambers are (1) the sinus venosus consisting of the right and left horn, which rise to the right atria and vein, (2) primitive atria which develop into some of the right atrium and all of the left atrium, (3) primitive ventricle that will form the left , (4)the bulbus cordis, which give rise to the right ventricle and some out flow tracts and (5) the paired dorsal aorta. The primitive heart begins to pump even before the heart tube fuse together, and by the day 22 contraction begin in the venosus and move through the heart in peristaltic-like wave. Mesenchyme surrounding the heart tube thickens to form a myoepicardial mantle, which is contractile and later gives rise to the myocardium, forming the muscular wall and the epicardium or visceral pericardium, covering the outside of the tube. The endocardial tube, which later becomes the endothelial lining of the heart, is separated by gelatinous connective tissue called cardiac jelly. During third week, the heart undergoes a serious of looping movement, which changes the shape of the heart allowing the four presumptive chambers of the heart to be brought into their definitive position. This obviously has a profound effect on the direction of the blood flow through the heart tube and is also the first morphological sign of left\right asymmetry in the embryo. This looping is made possible by breaking down of the dorsal mesocardium, which suspends the developing heart from the dorsal body wall. Developing of U-shaped bulb ventricular loop is formed through differential growth where by the atrium and sinus venosus come to lie dorsal to the bulbus cordis and ventricle. The heart then bends laterally the right (dextral looping) to form the S-shaped tube allowing the atria to lie above the bulbus cordis. The basic, but internally unsegmented, heart shape is achieved by four and half weeks. The heart is then organized further in order to achieve first is septation of common atrium into the left and right, second is septation of common artrioventricular canal, third is division of the out-flow tract, and last is septation of the ventricle into left and right. (Kevin Coward et al, 2013)

2.3.3.5.1 Venous system: There are three paired veins that drain into heart at week four: the vitelline veins, the umblical veins and the common cardinal vein. The vitelline vein flows the yolk sac into the embryo and enter the sinus venosus after passing through the septum transversum. At the same time the endothelial primordium of the liver grows into the septum transversum. The venous system changes in the lower body because of the effect of the growing liver which surround the vitelline and the umblical vein. The ducts venosus develops with in the liver, forcing blood carried by the left umblical vein, which is high in oxygen, through the liver. This then drains into inferior vena cava to enter the right atrium via right sinus horn. The right umblical vein then regresses. The venous system also changes in the upper body. The anterior cardinal vein develops into paired jugular veins, and a new vessel called the left bronchiocephalic vein forms, which channels blood from the left upper into the right jugular and then into the superior vena cava which drains into the right atrium. (Kevin Coward et al, 2013)

2.3.3.5.2 Atrial system: Pairs of branchial arches form during the fourth and fifth weeks. Aortic arches arising from the aortic sac grow into these branchial arches. The aortic arches terminate in paired dorsal aorta that eventually fuse to form a single aorta lying caudal to the branchial arches. In total five pairs of the aortic arches will form (1,2,3,4,5,) but there are not all present at once. Is believe of that the aortic arch system is an evolutionary remnant. The aortic arch system starts to remodel to form the separate aortic and pulmonary trunks at the end of the fourth week. This is achieved by aortic arches 1,2 regressing quickly, while 3 give arise to the carotid arteries. Arches 4,5 form the aortic arch and pulmonary trunk. These is also connection between pulmonary arch 4, and aortic arch called ductus arteriosus, whose role is to bypass the pulmonary circulation before birth. (Kevin Coward, 2013)

Fetal blood circulation: Dramatic and clinically significant changes occur to the circulator and respiratory systems at birth. Here, we look at changes primarily of the circulatory system and how these changes prepare the baby for life outside the uterus. If we were to follow the flow of oxygenated blood in the fetus from the

placenta, we would start in the umbilical vein and track the blood moving towards the liver. Here, half the blood enters the liver itself and half is redirected by the ductus venosus directly into the inferior vena cava, bypassing the liver. The blood remains well oxygenated and continues to the right atrium, from which it may pass into the right ventricle in the expected manner or directly into the left atrium via the foramen ovale. Blood within the left atrium passes to the left ventricle and then into the aorta. Blood entering the right atrium from the superior vena cava and the coronary sinus is relatively poorly oxygenated. The small amount of blood that returns from the lungs to the left atrium is also poorly oxygenated. Mixing of this blood with the well oxygenated blood from the ductus venosus reduces the oxygen saturation somewhat. Blood within the right ventricle will leave the heart within the pulmonary artery, but most of that blood will pass through the ductus arteriosus and into the descending aorta. Almost all of the well oxygenated blood that entered the right side of the heart has avoided entering the pulmonary circulation of the lungs, and has instead passed to the developing brain and other parts of the body. (Kevin Coward, 2013)

Ductus Venosus: The umbilical arteries constrict after birth, preventing blood loss from the neonate. The umbilical cord is not cut and clipped immediately after birth, however, allowing blood to pass from the placenta back to the neonatal circulation through the umbilical vein. The ductus venosus shunted blood from the umbilical vein to the inferior vena cava during foetal life, bypassing the liver. After birth a sphincter at the umbilical vein end of the ductus venosus closes. The ductus venosus will slowly degenerate and become the ligamentum venosus. Once the umbilical circulation is terminated the umbilical vein will also degenerate and become the round ligament (or ligamentum teres hepatis) of the liver. This may be continuous with the ligamentum venosus. The umbilical arteries will persist in part as the superior vesical arteries, supplying the bladder, and the remainder will degenerate and become the median umbilical ligaments. (Kevin Coward 2013).

Ductus Arteriosus: The shunt formed by the ductus arteriosus between the pulmonary trunk and the aorta in fetal life causes blood rich in oxygen to bypass

the lungs, which have a very high vascular resistance during development. With birth, the first breath of air and early use of the lungs the pulmonary vascular resistance drops and blood flow to the lungs increases. An increase in oxygen saturation of the blood, bradykinin produced by the lungs, and a reduction in circulating prostaglandins cause the smooth muscle of the wall of the ductus arteriosus to contract, restricting blood flow here and increasing blood flow through the pulmonary arteries. Physiological closure is normally achieved within 15 hours of birth. During the first few months of life, the ductus arteriosus closes anatomically, leaving the ligamentum arteriosum as a remnant. (Samuel et al, 2016)

As this is a remnant of the sixth aortic arch the left recurrent laryngeal nerve can be found here. The direction in which blood flows into the right atrium from the inferior vena cava and the crista dividens (the lower edge of the septum secundum, forming the superior edge of the foramen ovale) preferentially direct the flow of blood through the foramen ovale into the left atrium, reducing mixing with poorly oxygenated blood entering the right atrium from the superior vena cava. As the child takes his or her first breath the reduction in pulmonary vascular resistance and subsequent flow of blood through the pulmonary circulation increases the pressure in the left atrium. As the pressure in the left atrium is now higher than in the right atrium the septum primum is pushed up again the septum secundum, thus functionally closing the foramen ovale. Anatomical closure is usually completed within the next 6 months. In the adult the heart depression called the fossa ovalis remains upon the interior of the right atrium. (Samuel et al, 2016)

2.3.3.6 The Respiratory System: Is an outgrowth of the ventral wall of the foregut, and the epithelium of the larynx, trachea, bronchi, and alveoli originates in the endoderm. The cartilaginous, muscular, and connective tissue components arise in the mesoderm. In the fourth week of development, the tracheoesophageal septum separates the trachea from the foregut, dividing the foregut into the lung bud anteriorly and the esophagus posteriorly. Contact between the two is

maintained through the larynx, which is formed by tissue of the fourth and sixth pharyngeal arches. (Steven. M. Penny 2011).

The lung bud develops into two main bronchi: the right forms three secondary bronchi and three lobes; the left forms two secondary bronchi and two lobes. Faulty partitioning of the foregut by the tracheoesophageal septum causes esophageal atresias and TEFs. After a pseudoglandular (5 to 16 weeks), and canalicular (16 to 26 weeks) phase, cells of the cuboidal-lined respiratory bronchioles change into thin, flat cells, type I alveolar epithelial cells, intimately associated with blood and lymph capillaries. In the seventh month, gas exchange between the blood and air in the primitive alveoli is possible. Before birth, the lungs are filled with fluid with little protein, some mucus, and surfactant, which is produced by type II alveolar epithelial cells and which forms a phospholipid coat on the alveolar membranes. At the beginning of respiration, the lung fluid is resorbed except for the surfactant coat, which prevents the collapse of the alveoli during expiration by reducing the surface tension at the air– blood capillary interface. Absent or insufficient surfactant in the premature baby causes respiratory distress syndrome (RDS) because of collapse of the primitive alveoli (hyaline membrane disease). Growth of the lungs after birth is primarily due to an increase in the number of respiratory bronchioles and alveoli and not to an increase in the size of the alveoli. New alveoli are formed during the first 10 years of postnatal life. (Steven. M. Penny, 2011).

2.3.3.7 The Digestive System: The epithelium of the digestive system and the parenchyma of its derivatives originate from endoderm; connective tissue, muscular components, and peritoneal components originate in the mesoderm. The differentiation of the gut and its derivatives depends upon reciprocal interactions between the gut endoderm (epithelium) and its surrounding mesoderm (an epithelial-mesenchymal interaction). The gut system extends from the oropharyngeal membrane to the cloacal membrane and is divided into the pharyngeal gut, foregut, midgut, and hindgut. The pharyngeal gut gives rise to the pharynx and related glands. The foregut gives rise to the esophagus, the trachea

and lung buds, the stomach, and the duodenum proximal to the entrance of the bile duct. In addition, the liver, pancreas, and biliary apparatus develop as outgrowths of the endodermal epithelium of the upper part of the duodenum. Since the upper part of the foregut is divided by a septum (the tracheoesophageal septum) into the esophagus posteriorly and the trachea and lung buds anteriorly, deviation of the septum may result in abnormal openings between the trachea and esophagus. The epithelial liver cords and biliary system growing out into the septum transversum differentiate into parenchyma. Hematopoietic cells (present in the liver in greater numbers before birth than afterward), the Kupffer cells, and connective tissue cells originate in the mesoderm. The pancreas develops from a ventral bud and a dorsal bud that later fuse to form the definitive pancreas. Sometimes, the two parts surround the duodenum (annular pancreas), causing constriction of the gut. The midgut forms the primary intestinal loop, gives rise to the duodenum distal to the entrance of the bile duct, and continues to the junction of the proximal two-thirds of the transverse colon with the distal third. At its apex, the primary loop remains temporarily in open connection with the yolk sac through the vitelline duct. During the sixth week, the loop grows so rapidly that it protrudes into the umbilical cord (physiological herniation). During the 10th week, it returns into the abdominal cavity. While these processes are occurring, the midgut loop rotates 270° counterclockwise. Remnants of the vitelline duct, failure of the midgut to return to the abdominal cavity, mal rotation, stenosis, and duplication of parts of the gut are common abnormalities. The hindgut gives rise to the region from the distal third of the transverse colon to the upper part of the anal canal; the distal part of the anal canal originates from ectoderm. The hindgut enters the posterior region of the cloaca (future anorectal canal), and the allantois enters the anterior region (future urogenital sinus). The urorectal septum will divide the two regions, and breakdown of the cloacal membrane covering this area will provide communication to the exterior for the anus and urogenital sinus. Abnormalities in the size of the posterior region of the cloaca shift the entrance of the anus anteriorly, causing rectovaginal and rectourethral fistulas and atresias. The anal canal itself is derived from

endoderm (cranial part) and ectoderm (caudal part). The caudal part is formed by invaginating ectoderm around the proctodeum. Vascular supply to the anal canal reflects its dual origin. Thus, the cranial part is supplied by the superior rectal artery from the inferior mesenteric artery, the artery of the hindgut, whereas the caudal part is supplied by the inferior rectal artery, a branch of the internal pudendal artery. (W.T Sadler et al, 2012).

2.3.3.8 Urogenital System: The urinary and genital systems both develop from mesodermal tissue. Three urinary system develop in a temporal sequence from cranial to caudal segments. The pronephrose, which forms in the cervical region, is vestigial. The mesonephros, which forms in the thoracic and lumbar region, is large and is characterized by excretory units (nephrons) and its own collecting duct, the mesonephricor wolffian duct. In the human, it may function briefly, but most of the system disappears. Duct and tubules from the mesonephrone form the conduit for sperm from the testes to the urethra. In the male, these ducts regress. The metanephros, or permanent kidney, develops from two sources. It from its own excretory tubules or nephrons like other system, but its collecting system originates from the ureteric but, an outgrowth of the mesonephric duct. This gives rise to the ureter, renal pelvis, calyces, and the entire collecting system. Connection between the collecting and excretory tubule system is essential for normal development. (W.T Sadler 2012).

2.3.3.9 Fetal Membrane and Placenta: The placenta is the organ that facilitates nutried and gas exchange between the maternal and fetal compartment. (Ash Monga et al, 2011).

2.3.3.9.1 Structure of the Placenta: By the beginning of the fourth month, the placenta has two components: a fetal portion, formed by the chorion frondosum and a maternal portion, formed by the decidua basalis. On the fetal side, the placenta is bordered by the chorionic plate, on its maternal side, it is bordered by the decidua basalis, of which the decidual plate is most intimately incorporated into the placenta. In the junctional zone, trophoblast and decidual cells intermingle. Between the chorionic and decidual plates are the intervillous spaces, which are

filled with maternal blood. They are derived from lacunae in the syncytiotrophoblast and are lined with syncytium of fetal origin. The villous trees grow into the intervillous blood lakes. (Ash Monga et al, 2011).

During the fourth and fifth months, the decidua forms a number of decidual septa, which project into intervillous spaces but do not reach the chorionic plate. These septa have a core of maternal tissue, but their surface is covered by a layer of syncytial cells, so that at all times, a syncytial layer separates maternal blood in intervillous lakes from fetal tissue of the villi. As a result of this septum formation, the placenta is divided into a number of compartments, or cotyledons. As a result of the continuous growth of the fetus and expansion of the uterus, the placenta also enlarges. Its increase in surface area degenerated. Between the chorionic and decidual plates are the intervillous spaces, which are filled with maternal blood. They are derived from lacunae in the syncytiotrophoblast and are lined with syncytium of fetal origin. The villous trees grow into the intervillous blood lakes. Because the decidual septa do not reach the chorionic plate, contact between intervillous spaces in the various cotyledons is maintained. Its increase in surface area roughly parallels that of the expanding uterus, and throughout pregnancy, it covers approximately 15% to 30% of the internal surface of the uterus. (Ash Monga et al, 2011).

2.3.3.9.2 Full-Term Placenta: At full term, the placenta is discoid with a diameter of 15 to 25 cm, is approximately 3 cm thick, and weighs about 500 to 600 g. At birth, it is torn from the uterine wall and, approximately 30 minutes after birth of the child, is expelled from the uterine cavity as the afterbirth. When the placenta is viewed from the maternal side, 15 to 20 slightly bulging areas, the cotyledons, covered by a thin layer of decidua basalis, are clearly recognizable. The fetal surface of the placenta is covered entirely by the chorionic plate. A number of large arteries and veins, the chorionic vessels, converge toward the umbilical cord (The chorion, in turn, is covered by the amnion. Attachment of the umbilical cord is usually eccentric and occasionally even marginal. Rarely, however, does it insert

into the chorionic membranes outside the placenta (velamentous insertion). (Ash Monga et al, 2011).

Circulation of the Placenta Cotyledons receive their blood through 80 to 100 spiral arteries that pierce the decidual plate and enter the intervillous spaces at more or less regular intervals. Collectively, the intervillous spaces of a mature placenta contain approximately 150mL of blood, which replenished about three or four times per minute. This blood moves along the chorionic villi, which have surface area of 4 to 14m2. Placenta exchange does not take place in all villi, only in those that have fetal vessels in contact with the covering syncytial membrane. The placenta membrane separates the maternal and fetal blood is composed of four layers: the endothelial lining of fetal vessels, the connective tissue in the villi, the trophoblastic layer, the syncytium. Normally, there is no mixing of maternal and fetal blood. (Ash Monga et al, 2011).

2.3.3.9.3 Function of Placenta: Main functions of placenta: exchange of metabolic and gaseous products between the maternal and fetal blood streams, production of hormone. (Steven. M. Penny 2011).

Exchanges of gasses: Such as oxygen, carbon oxide, and carbon mono-oxide and this accomplished by simple diffusion. (Steven. M. Penny, 2011).

Exchange of Nutrients and Electrolytes: Such as amino acids, free fatty acids, carbohydrates, and vitamins is rapid and increase as pregnancy advance. (Steven. M. Penny, 2011).

Production of Hormones: By the end of the four month the placenta produces the progesterone, estrogenic hormones, predominately estriol, until just before the end of pregnancy when a maximum level is reached which simulates uterine growth and development of mammary glands. During the first **2** month of pregnancy the syncytiotrophoblast also produce human chorionic gonadotropin (Hcg), which maintain the corpus luteum. Also, placenta produces somatomammotropin. It is a growth-hormone-like substant that gives the fetus the priority on maternal blood glucose and make mother somewhat diabetogenic. Also promotes breast development for milk production. (Steven. M. Penny, 2011).

At the end of pregnancy, a number of changes that occur in the placenta may indicate reduced exchange between the two circulations. These changes include: increase in fibrous tissue in the core of villus, thickening of the basement membrane in fetal capillaries, obliterative changes in small capillaries of the villi, deposition of fibrinoid on the surface of the villi in the junctional zone and in the chorionic plate. (Steven. M. Penny, 2011).

2.3.3.9.4 Complications of Placenta which may occur due to DM/HT:

Placenta Previa: In placenta previa, the placenta is located over or very near the internal os. This condition complicates as many as 1 in 200 deliveries. Although half of women are near term when bleeding first develops, preterm delivery still poses a formidable problem for the remainder, because not all women with placenta previa and a preterm fetus can be treated expectantly. From the perspective of the mother, adequate blood transfusion and cesarean delivery have resulted in a marked reduction in mortality from placenta previa. (Kenneth J. Leveno et al, 2013)

Classification of Placenta Previa:

- Total placenta previa: The internal cervical os is covered completely by placenta.
- Partial placenta previa: The internal os is partially covered by placenta
- Marginal placenta previa: The edge of the placenta is at the margin of the internal os.
- Low-lying placenta: The placenta is implanted in the lower uterine segment such that the placental edge actually does not reach the internal os but is in close proximity to it (Kenneth J. Leveno et al, 2013).

U/S studies done earlier in this pregnancy are invaluable. A midline longitudinal scan is used before and after evacuating a full bladder in order to minimize distortion of lower uterine segment. Translabial or TVS may be used if technical difficulties are there. (Alpesh Gandhi et al, 2016)

Vasa Previa: Another condition, termed vasa previa, is diagnosed when the fetal vessels course through membranes and are present at the cervical os. With vasa previa, there is considerable danger to the fetus, for rupture of the membranes may be accompanied by rupture of a fetal vessel, causing exsanguination. Unfortunately, the amount of fetal blood that can be shed without killing the fetus is relatively small. A quick, readily available approach for detecting fetal blood is to smear the blood on a glass slide, stain the smear with Wright stain, and examine for nucleated red cells, which normally are present in cord blood but not maternal blood. (Kenneth J. Leveno et al, 2013)

Placenta Accreta, Increta, and Percreta: As many as 7 percent of cases of placenta previa may be associated with placenta accreta or one of its more advanced forms, placenta increta or percreta. Such abnormally firm attachment of the placenta might be anticipated because of poorly developed decidua in the lower uterine segment associated with placenta previa. (Kenneth J. Leveno et al, 2013)

Placenta accreta can be diagnosed by U/S, mostly by the absence of retroplacental hypoechogenic zone of the decidua/myometrium. (Alpesh Gandhi et al, 2016)

2.3.3.10 Amniotic Fluid: The amniotic cavity is filled with clear watery fluid that is produced in part by amniotic cell but is derived primarily from maternal blood. The amount increases from approximately 30 ml at first ten week to 450ml at 20 weeks to 800-1000ml at 37 weeks. The volume of amniotic fluid is replaced every 3 hours. From the 5^{th} month fetus swallows its own amniotic fluid and it is estimated that it drinks about 400ml a day, about half of the total amount. Fetal urine is added daily to the amniotic fluid in the 5^{th} month, but this urine is mostly water, because the placenta is functioning as an exchange for metabolic wastes. Function of Amniotic Fluid: absorbs jolts, prevent adherence of the embryo to amnion, allows for fetal movements (T.W Sadler et al, 2012).

2.3.3.10.1 Oligohydramnios: Normally, amniotic fluid volume increases to about 1 L by 36 weeks and decreases thereafter to only 100 to 200 mL or less post-term. In rare instances, the volume of amniotic fluid may fall far below the normal limits and occasionally be reduced to only a few milliliters. Diminished fluid volume is

termed oligohydramnios and is sonographically defined as an amniotic fluid index (AFI) of 5 cm or less in general, oligohydramnios developing early in pregnancy is less common and frequently has a bad prognosis. By contrast, diminished fluid volume may be found often with pregnancies that continue beyond term. The risk of cord compression, and in turn fetal distress, is increased with diminished amniotic fluid in all labors, but especially in post-term pregnancy. An amniotic fluid index of less than 5 cm after 34 weeks is associated with an increased risk of adverse perinatal outcomes. For example, a pregnancy with an intrapartum amniotic fluid index of less than 5 cm is at an increased risk for variable fetal heart rate decelerations, cesarean delivery for fetal distress, and 5-minute Apgar score of less than 7. (Kenneth J. Leveno et al, 2013)

The causes of oligohydramnios such as chromosomal abnormalities, congenital anomalies, growth restriction, intrauterine fetal death, post-term pregnancy, ruptured membranes, placenta abruption, twin–twin transfusion, utero-placental insufficiency, hypertension, preeclampsia, diabetes, drugs such as (Prostaglandin synthase inhibitors, Angiotensin-converting enzyme inhibitors), and due to Idiopathic causes. (Kenneth J. Leveno2013)

2.3.3.10.2 Polyhydramnios: More than 2000 mL of amniotic fluid is considered excessive and is termed polyhydramnios and sometimes called hydramnios. In rare instances, the uterus may contain an enormous quantity of fluid 15L. A minor-to-moderate degrees of polyhydramnios is 2L to 3L, are rather common and are identified in about 1 percent of all pregnancies. Sonographically, polyhydramnios is most commonly defined as an amniotic fluid index (AFI) of greater than 24 or 25cm corresponding to greater than either the 95th or 97.5th percentiles. Polyhydramnios has also been defined by ultrasound measurement of the deepest vertical pocket of fluid. In this system, severe polyhydramnios is defined by a free-floating fetus found in pockets of fluid of 16 cm or greater. (Kenneth J.Leveno et al, 2013)

Causes of polyhydramnios are frequently associated with fetal malformations, especially of the central nervous system or gastrointestinal tract. For example,

polyhydramnios accompanies about half of cases of anencephaly and esophageal atresia. A fetal anomaly is identified in almost half of cases with moderate or severe polyhydramnios. (Kenneth J.Leveno et al, 2013)

2.3.4 Birth Defects & Prenatal Diagnosis:

Birth defect, congenital malformation, and congenital anomaly are synonymous terms used to describe structural, behavioral, functional, and metabolic disorders present at birth. Major structural anomalies occur in approximately 3% of live born infants and birth defects are a leading cause of infant mortality, accounting for approximately 25% of infant deaths. Minor Anomalies occur in approximately 15% of newborns. These structural abnormalities, such as microtia (small ears), pigmented spots, and short palpebral fissures, are not themselves detrimental to health but, in some cases, are associated with major defects. For example, infants with one minor anomaly have a 3% chance of having a major malformation; those with two minor anomalies have a 10% chance; and those with three or more minor anomalies have a 20% chance. Therefore, minor anomalies serve as clues for diagnosing more serious underlying defects. In particular, ear anomalies are easily recognizable indicators of other defects and are observed in virtually all children with syndromic malformations. (Kenneth J.Leveno et al, 2013)

2.3.4.1 Types of Abnormalities:

- Malformations**:** Occur during formation of structures (during organogenesis). They may result in complete or partial absence of a structure or in alterations of its normal configuration. Malformations are caused by environmental and/or genetic factors acting independently or in concert. Most malformations have their origin during the third to eighth weeks of gestation. (Kenneth J.Leveno et al, 2013).
- Disruptions: Result in morphological alterations of already formed structures and are caused by destructive processes. Vascular accidents leading to transverse limb defects and defects produced by amniotic bands are

examples of destructive factors that produce disruptions. (Kenneth J.Leveno et al, 2013).

- Deformations: Result from mechanical forces that mold a part of the fetus over a prolonged period. Clubfeet, for example, are caused by compression in the amniotic cavity. Deformations often involve the musculoskeletal system and may be reversible postnatally. (Kenneth J.Leveno et al, 2013).
- Syndrome**:** Is a group of anomalies occurring together that have a specific common cause. An example is the VACTERL association (vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies). (Kenneth J.Leveno et al, 2013).

2.3.4.2 Factors That Affect in Birth Defects:

There are many factors that may affect in pregnancy leading to birth defect such as environmental Factors, infectious agent (rubella, cytomegalovirus, herpes simplex virus, varicella virus), toxoplasmosis, radiation, pharmaceutical drugs and chemical, maternal disease (DM, phenylketonuria, and HT), nutritional deficiencies, obesity, hypoxia, heavy metal, chromosomal and genetic factors.(Kenneth J. Leveno et al, 2013).

2.3.4.3 Birth Defect:

Routine first trimester dating scanning has a number of benefits (1) it is more accurate at assessing gestational age than menstrual periods, and therefore reduces the rates of induction of labour for post-term pregnancies (2) detects multiple pregnancies early in pregnancy and (3) can detect some major structural anomalies such as anencephaly. However, a more detailed, although limited, anomaly scan is incorporated into a NT scan such as the shape of the fetal skull, presence of nose, hands and feet and presence of stomach and bladder. Therefore, instigation of Down's syndrome screening strategies such as the Combined or Integrated test which involve an NT scan are likely to not only increase the detection of aneuploidy but also major structural anomalies and particularly cardiac defects

earlier in gestation. In the UK there is a policy of routine second trimester ultrasound screening for fetal anomalies. However, detection of fetal anomalies varies considerably depending on the anomaly being screened for as well as the gestation at screening, the skill of the operator and the quality of the equipment used. A systematic review of routine ultrasound screening for fetal anomalies included 96,633 babies between 1996 and 1998. The overall detection rate was 44.7% with detection being considerably higher <24 weeks (41.3%) than >24 weeks (18.6%). In the UK although the detection rates appear to be higher there is a considerable geographic variation. Chitty et al. reported an overall detection rate of 74% in an inner London unit, whereas Boyd et al. reported a detection rate of 50% in Oxford. The detection of cardiac anomalies is of particular interest. (Kieth Edmond, 2007)

Early prenatal detection of congenital heart disease (CHD) has increased due to advances in ultrasound resolution and the incorporation of at least a 4-chamber cardiac view in the routine anomaly scan, which is now accepted as standard in the UK. There is, however, regional variation in antenatal detection of CHD, with those obstetric centers close to cardiac units faring better than those situated in more remote areas. There also appears to be a discrepancy between countries, which reflect different obstetric practice; for example, the policy of universal anomaly scanning between 20 and 22 weeks in the UK compared with targeted anomaly scanning in the USA. However, cardiac anomalies are the commonest type of structural anomalies detected in fetal life and at birth with a frequency of 8:1000. (Kieth Edmond, 2007)**.**

2.3.4.3.1 The Craniofacial Defect and Skeletal Dysplasia:

- **Cranioschisis**: In some cases, the cranial vault fails to form, and brain tissue exposed to amniotic fluid degenerates, resulting in anencephaly. It is caused by failure of cranial neuropore to close. (Bruce M. Carlson, 2014)
- **Craniosynostosis:** It is caused by premature closure of one or more sutures. It occurs 1 in 2500 birth and is a feature of more than 100 genetic

syndromes. The shape of skull depends on one of the sutures is closed (57\100 of cases) result in frontal and occipital expantion, and skull become narrow and long. (Bruce M. Carlson, 2014)

- **Brachycephally:** Premature closure of coronal suture results in the a short skull. (Bruce M. Carlson, 2014)
- **Plagiochephaly:** Asymmetry flatting result from premature closure of the coronal suture on one side. (Bruce M. Carlson, 2014)

2.3.4.3.2 Ear Defects:

- **Congenital Hearing Loss:** May be caused by abnormal development of membranous and bony labyrinths or by malformation of the auditory ossicles and eardrum. In the most extreme cases, the tympanic cavity and external meatus are absent. (Bruce M. Carlson, 2014)
- **External Ear Defect:** Are common, they include minor and severe abnormalities. They often associated with other malformations. All of the frequently occurring chromosomal syndromes are most of the less common ones have ear anomalies as one of their characteristics. The common type of external ear defect is: preauricular appendages and pits which is skin tags and shallow depressions, respectively, anterior to the ear. Pits may indicate abnormal development of the auricular hillocks, whereas appendages may be caused by accessory hillocks. Like other external ear defects, both are sometimes associated with other malformations (Bruce M. Carlson, 2014).

2.3.4.3.3 Eye Defects:

- **Coloboma:** May occur if the choroid fissure fails to close. Normally, this tissue closes during the seventh week of development. When it does not, a cleft persist. Although such a cleft is usually in the iris only. (Bruce M. Carlson, 2014)
- **Coloboma Iridis:** It may extend into the ciliary body, the retina, the choroid, and the optic nerve. Coloboma is a common eye abnormality frequently

associated with other eye defects. Colobomas (cleft) of thee eye lids may also occur. Mutations in the PAX2 gene have been linked with nerve colobomas and may be play a role in the other types as well. Renal defects also occur with mutation in PAX2 as part of the renal coloboma syndrome. (Bruce M. Carlson, 2014)

- **Congenital Cataracts**: Cause the lens to become opaque during intrauterine life. Although this anomaly is usually genetically determined, many children born to others who had rubella (German measles) between the fourth and seven weeks of pregnancy had cataracts. If the mother is infected after the seventh weeks of pregnancy, the lens escapes damage, but the child may have hearing loss as a result of cochlear abnormalities. (Bruce M. Carlson, 2014)

2.3.4.3.4 Head defect:

2.3.4.3.4.1 Ventriculomegaly and Hydrocephalus: The abnormal enlarge of the ventricles within the brain is referred to as ventriculomegaly. Hydrocephalus is typically reserved for the cases of ventriculomegaly that are more severe and are caused by some type of obstruction to the flow of cerebro spinal fluid (CSF). Therefore, obstructive hydrocephalus is the buildup of CSF within the ventricular system secondary to some type of obstruction. Ventriculomegaly has been cited as the most common cranial abnormality. Suspicion of ventricular dilatation occurs when the atrial diameter measures more than 10 mm. The sonographic finding of the "dangling choroid" sign describes the echogenic choroid plexus, hanging limp, and surrounded by CSF, within the dilated lateral ventricle. Hydrocephalus can be described as mild, moderate, or severe. There are two main types of hydrocephalus, communicating and noncommunicating. Communicating hydrocephalus is apparent when the obstruction lies outside of the ventricular system, whereas noncommunicating hydrocephalus is when the obstruction level is located within the ventricular system. Although hemorrhagic obstruction and the subsequent enlargement of the ventricles can occur in utero, congenital obstruction

of the ventricular system, by means of aqueductal stenosis, remains the most common cause of hydrocephalus in utero. There are also other etiologies of hydrocephalus, including many chromosomal aberrations and intrauterine infections. (Kenneth J.Leveno et al, 2013).

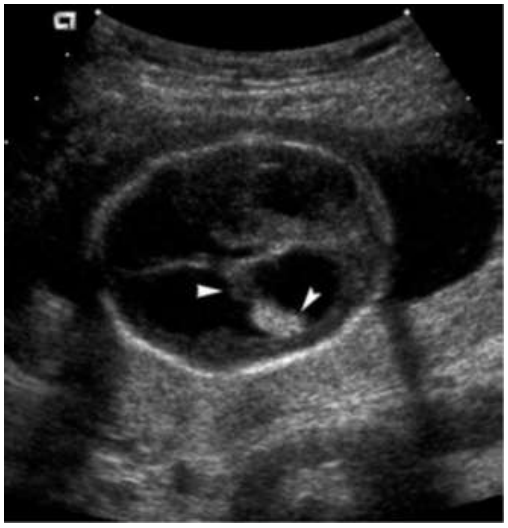
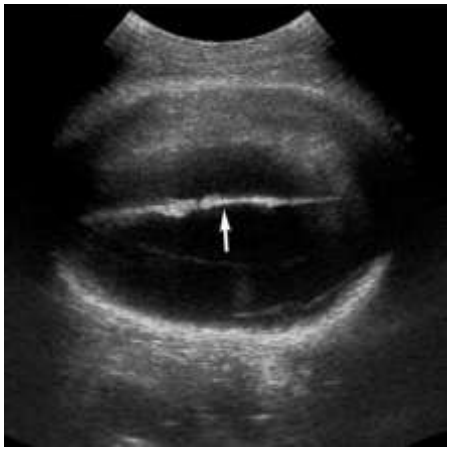


Figure (2.7) Dangling choroid sign. Axial view of the fetal cranium with ventriculomegaly demonstrates choroid plexus (arrowheads) dangling within the dilated ventricle (T.W Sadler et al, 2012)

2.3.4.3.4.2 Aqueductal Stenosis: Aqueductal stenosis is the most common cause of hydrocephalus in utero. The cerebral aqueduct (aqueduct of Sylvius), located between the third and fourth ventricle of the brain, may be narrowed, thus preventing the flow of CSF from the third to the fourth ventricle. This obstruction level will cause the third ventricle and both lateral ventricles to expand whereas the fourth ventricle remains normal. (Kenneth J.Leveno et al, 2013).

2.3.4.3.4.3 Hydranencephaly: Hydranencephaly is a fatal condition in which the entire cerebrum is replaced by a large sac containing CSF. With hydranencephaly, the falx cerebri may be partially or completely absent, whereas the brain stem and basal ganglia are maintained and surrounded by CSF. There will be no cerebral cortex identified. There have been several postulations regarding the cause of hydranencephaly, including bilateral occlusion of the internal carotid arteries with subsequent destruction of the cerebral hemispheres. Another hypothesis is that

intrauterine infections such as cytomegalovirus and toxoplasmosis lead to the destruction of the cerebral hemispheres. Hydranencephaly can be difficult to differentiate with the sonographic findings of hydrocephalus and alobar holoprosencephaly. It is important to note that with both hydrocephalus and holoprosencephaly there will be a rim of cerebral tissue maintained, whereas with hydranencephaly there is no cerebral mantle present. Hydranencephaly is typically a fatal condition, with death occurring in the first year of life. (Kenneth J.Leveno et al, 2013).



67023 Figure (2.8)

Hydranencephaly. This axial image of a fetus demonstrates a fluid-filled cranium with no visible cerebral cortex. Part of the falx cerebri (arrow) is noted within the midline of the brain. All findings are consistent with hydranencephaly (T.W. Sadler et al, 2012)

2.3.4.3.4.4 Holoprosencephaly: Holoprosencephaly is a midline brain anomaly that is associated with not only brain aberrations but also atypical facial structures. It may be detected with endovaginal imaging as early as the first trimester. There are three main types of holoprosencephaly: alobar, semilobar, and lobar. Although the lobar form can be consistent with life, alobar holoprosencephaly is the most severe form, often resulting in neonatal death. Alobar holoprosencephaly is diagnosed when there is absence of the corpus callosum, CSP, third ventricle, interhemispheric fissure, and falx cerebri. There will also be evidence of a

horseshoe shaped monoventricle and the lobes of the thalamus may be fused and echogenic in appearance. Conversely, the cerebellum and brain stem remain intact. Cyclopia, a condition in which the orbits are fused and contain a single eye, and proboscis, a false nose situated above the orbits, are two of the most disturbing external findings associated with holoprosencephaly. Other facial anomalies such as anophthalmia, hypotelorism, median cleft lip, and cebocephaly may be detected during a fetal sonogram as well. With the less devastating forms of holoprosencephaly, such as lobar, there are varying degrees of fusion of the midline structures. Infants with lobar holoprosencephaly may experience severe mental retardation. Trisomy 13, or Patau syndrome, is present in 50% to 70% of fetuses diagnosed with holoprosencephaly. (Bruce M. Carlson, 2014)

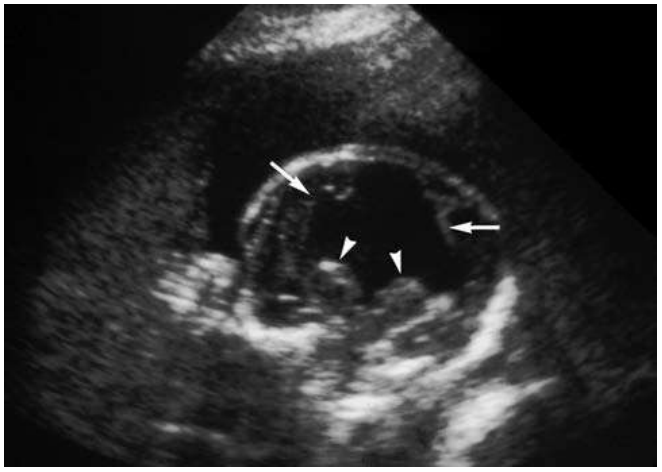


Figure (2.9) Holoprosencephaly. Coronal image of a head demonstrates fusion of the lateral ventricles (arrows). This is referred to as a monoventricle. The thalami are partially splayed (arrowheads), and the falx cerebri is absent. (Ash Monga et al, 2013)

2.3.4.3.4.5 Dandy–Walker Malformation & Mega Cisterna Magna: Dandy–Walker malformation (DWM) is actually a classification within a larger group of anomalies referred to as the Dandy–Walker complex. Dandy–Walker complex is a spectrum of posterior fossa abnormalities that involve the cystic dilatation of the cisterna magna and fourth ventricle. DWM is thought to be caused by a developmental abnormality in the roof of the fourth ventricle. The sonographic findings of DWM include an enlarged cisterna magna that communicates with a

distended fourth ventricle through a defect in the cerebellum. The cerebellar vermis is either completely absent or hypoplastic. As a result, the tentorium, the structure that separates the cerebrum from the cerebellum, is elevated. There are often other midline brain abnormalities present as well. For instance, agenesis of the corpus callosum, ventriculomegaly, holoprosencephaly, and cephaloceles are all associated anomalies that can co-exist with DWM. Mega cisterna magna, which is the enlargement of the cisterna magna without the involvement of the fourth ventricle, may be confused with Dandy–Walker malformation. Mega cisterna magna is present when only the cisterna magna is enlarged, measuring more than 10 mm in depth. Consequently, the fourth ventricle is normal with mega cisterna magna and enlarged with DWM. It is important to note that in the early second trimester, the inferior portion of the cerebellar vermis may not be formed, thus making it appear as if the fetus has partial agenesis of the vermis. For that reason, care must be taken to visualize an intact cerebellar vemis.1 If the cerebellar vermis is absent and the fourth ventricle is enlarged, then Dandy–Walker malformation must be suspected. (Bruce M. Carlson, 2014).

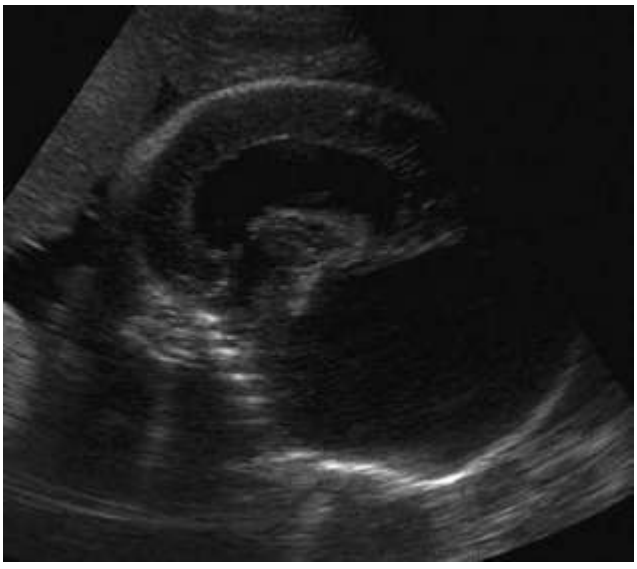


Figure (2.10) Sagittal image of Dandy–Walker malformation. This sagittal image of the fetal cranium demonstrates an enlarged posterior fossa. (Ash Monga et al, 2013

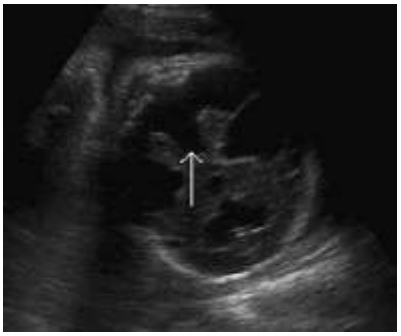


Figure (2.11) Axial image of Dandy–Walker malformation. The dilated fourth ventricle (arrow) is seen between the splayed lobes of the cerebellum, a finding consistent with Dandy–Walker malformation (Ash Monga et al, 2013)

2.3.4.3.4.6 Agenesis of the Corpus Callosum & Cavum Septum Pellucidum: The corpus callosum is a bridge of tissue located within the midline of the brain that connects the two cerebral hemispheres. It functionally provides a pathway for communication between the hemispheres and is completely formed by 18 weeks. The CSP**,** located inferior to the corpus callosum, and the corpus callosum develop at the same time. The congenital lack of these structures is termed agenesis, as in agenesis of the corpus callosum, and CSP. There are several distinct sonographic findings consistent with agenesis of the corpus callosum, excluding the obvious absence of this structure. The "sunburst" manifestation of the sulci is a straightforward and discernible sonographic finding. In the normal brain, the sulci within the cerebrum typically travel parallel to the corpus callosum, but with agenesis of the corpus callosum they tend to have a more perpendicular or radial arrangement and often appear to have a "spoke wheel" pattern. Colpocephaly, small frontal horns and enlarged occipital horns, is often present as well and offers a distinct teardrop shape to the lateral ventricles. In addition, with absence of the CSP and corpus callosum the third ventricle tends to migrate more superiorly and anterior, or complete absence of the corpus callosum. Most often, if the corpus callosum is absent, the CSP will be Schizencephaly. Schizencephaly is associated with the development of fluid-filled clefts within the cerebrum. The etiology of schizencephaly is unknown and few cases have been reported. The sonographic appearance of schizencephaly is that of a cerebrum containing clefts filled with

anechoic, CSF. There are several associated anomalies such as agenesis of the corpus callosum, agenesis of the CSP, sent as well. Their nonexistence has been linked to as many as 50 to 200 different syndromes and anomalies such as holoprosencephaly, Dandy–Walker malformation, aqueductal stenosis, trisomy 18, and trisomy 13.1,2 appear dilated. (Kevin Coward et al, 2013)

2.3.4.3.4.7 Porencephaly: Is a rare condition in which a cyst communicates with the ventricular system. Porencephaly can occur after the fetus has experienced hemorrhage within one or both of the cerebral hemispheres. As the hemorrhage changes states, it will form into a cystic cavity and will eventually communicate with the lateral ventricle of the affected side. It is important to note that arachnoid cysts will not communicate with the ventricular system. (Kenneth J.Leveno et al, 2013).

2.3.4.3.4.8 Choroid Plexus Cysts: Choroid plexus cysts are cysts located within the choroid plexus of the lateral ventricles. These small cysts are frequently encountered during a routine sonographic examination and typically regress by the end of the third trimester, although they are associated with an increased risk of trisomy 18. A choroid plexus cyst will be located within the choroid plexus of the lateral ventricle, measure more than 2 mm, appear round and anechoic, and have smooth walls. (Kenneth J.Leveno et al , 2013).

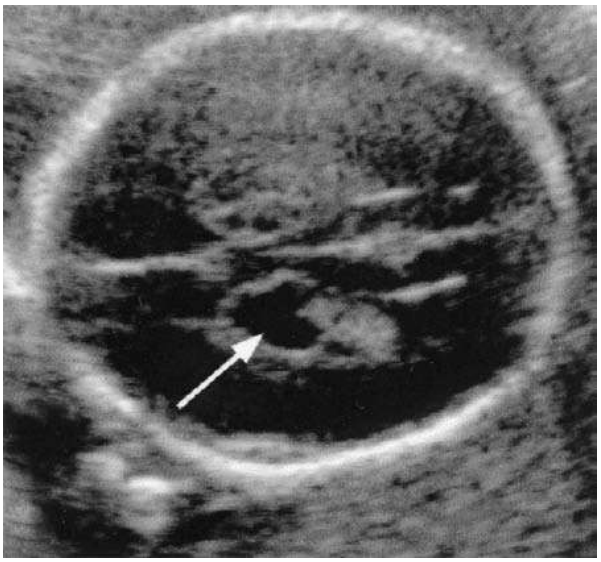
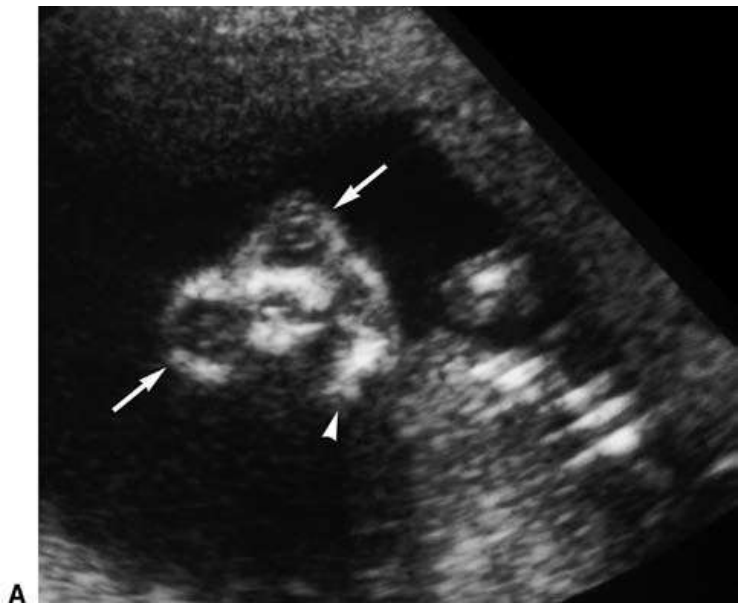


Figure (2.12) Choroid plexus cyst. This axial image demonstrates the sonographic appearance of a choroid plexus cyst (arrow) (Ash Monga et al, 2011)

2.3.4.3.5 Neural Tube Defects & Brain:

2.3.4.3.5.1Neural Tube Defects: Neural tube defects occur when the embryonic neural tube fails to close. Among the list of neural tube defects are cephaloceles, various spinal dysraphisms, anencephaly, and spina bifida. Anencephaly and spina bifida are the most common neural defects, occurring in 1 per 1,000 pregnancies. (Bruce M. Carlson, 2014)

- **Acrania:** Remains one of the most common neural tube defects. It is defined as the absence of the cranial vault above the bony orbits. It can be further divided into two main subtypes that are related to the amount of cerebral tissue present, anencephaly and exencephaly. Anencephaly is considered when there are no cerebral hemispheres present, whereas exencephaly denotes a normal amount of cerebral tissue, cranium is absent, the sonographic appearance of anencephaly has been described as having "froglike" faces, or bulging eyes, and absence of the cranial vault. (Bruce M. Carlson, 2014)



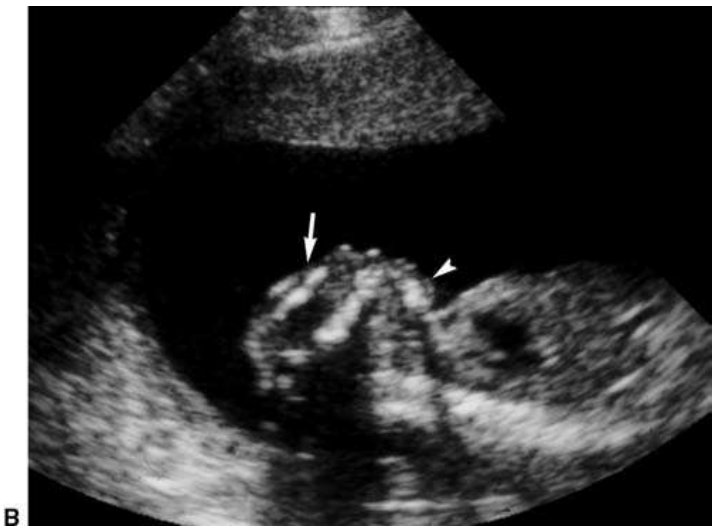


Figure (2.13) Anencephaly. A. Coronal image of the fetal face demonstrates absence of the forehead and cranium with the typical "froglike" faces (arrows) of anencephaly. The mandible is normally formed (arrowhead). B. Sagittal image of the same fetus demonstrates absence of the forehead and cranium (arrow). The mandible(arrowhead) and lower face appears normal (Ash Monga et al, 2011)

- **Arnold–Chiari II Malformation and Spina Bifida:** Arnold–Chiari II or Chiari II malformation is a group of cranial abnormalities associated with the neural tube defect spina bifida. Spina bifida may result in a mass that protrudes from the spine. This mass can be referred to as a meningocele or myelomeningocele, depending on its contents. The most common location of spina bifida is within the distal lumbosacral region. Several notable changes occur within the brain and skull with spina bifida. The frontal bones become flattened and will yield a lemon shape to the cranium, which is referred to as the "lemon" sign, often referred to as scalloping of the frontal bones. The cerebellum will become displaced inferiorly and posteriorly and appear curved in the presence of spina bifida, which is referred to as the "banana" sign. As a result of the cerebellum being displaced inferiorly, the cisterna magna is completely Cephaloceles. Cephaloceles are protrusions of intracranial contents through a defect in the skull. Cephaloceles can also be distinguished by their location. The most common location for a cephalocele is in the occipital region. However, cephaloceles may also have frontal and parietal positions. Cephaloceles are common findings in Meckel–Gruber

syndrome and have varying sonographic appearances based on their content can be performed. (Bruce M. Carlson 2014)

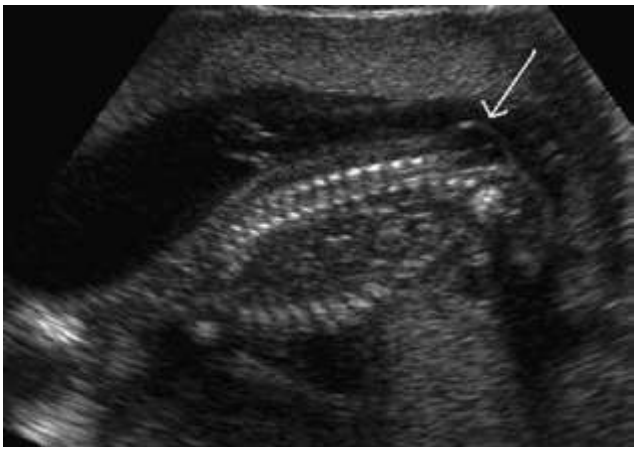


Figure (2.14) Myelomeningocele. This sagittal image of the fetal spine demonstrates a meningomyelocele (arrow) located in the distal spine (T.W Sadler et al, 2012)

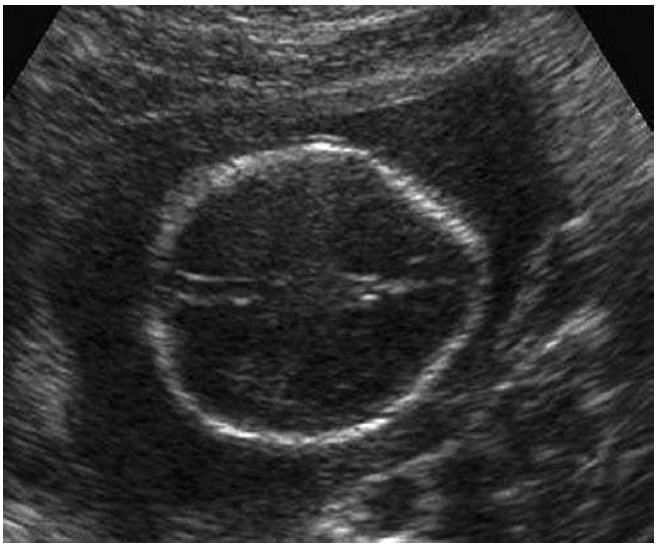


Figure (2.15) Lemon sign. Axial view of the fetal cranium demonstrates the lemon sign found in most cases of spina bifida (Samuel Webster et al, 2016)

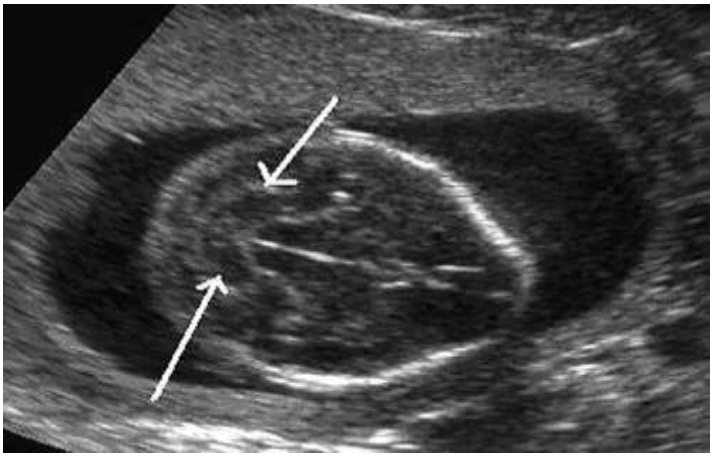


Figure (2.16) Banana sign. Axial view of the cerebellum demonstrates the abnormal banana shape that the cerebellum (arrows) takes in the presence of spina bifida (Samuel Webster et al, 2016).

2.3.4.3.5.2 Fetal Intracranial Tumors: The most common intracranial tumor found in utero is the teratoma. Teratomas contain tissues such as hair, sebum, and fat and most often appear as complex masses that distort the normal architecture of the brain. Choroid plexus papillomas are found within the choroid plexus and produce an increase in the production of CSF, which in turn leads to ventriculomegaly. Other sonographic findings associated with brain tumors are macrocephaly and intracranial calcifications. Corpus callosum lipomas may also be present with agenesis of the corpus callosum. A lipoma will appear as a solid echogenic mass. (T.W Sadler et al, 2012)

2.3.4.3.5.3 Fetal Intracranial Hemorrhage (Intraventricular Hemorrhage): Although intracranial hemorrhage is a common finding in premature infants weighing less than 1500 g and those born before 32 weeks gestation, it occurs less often in utero. Maternal use of cocaine, trauma, and a history of amniocentesis are all listed as predisposing condition of fetal intracranial hemorrhage; however, the most common risk factor for fetal intrauterine intracranial hemorrhage has been listed as maternal platelet disorders. Most often, the origin of intracranial hemorrhage, also referred to as intraventricular hemorrhage, is within the germinal matrix. The germinal matrix is a group of thin-walled, pressure-sensitive vessels located in the subependymal layer of the ventricles. These vessels are prone to rupture secondary to their thin walls. The hemorrhage can spread into the lateral ventricle, often leading to noncommunicating hydrocephalus, as the clot obstructs

the flow of CSF within the narrowed regions of the ventricular system. Hemorrhage can also occur with obliterated Posterior fossa abnormalities. (T.W Sadler et al, 2012)

2.3.4.3.5.4 Cephaloceles: Cephaloceles are protrusions of intracranial contents through a defect in the skull provides a description of the different types of cephaloceles based on their content. Cephaloceles can also be distinguished by their location. The most common location for a cephalocele is in the occipital region. However, cephaloceles may also have frontal and parietal position be performed. Although cytomegalovirus has been listed as the most common in utero infection, other infections, such as toxoplasmosis, rubella, parvovirus, varicella zoster, and Herpes simplex, occur less often but may have devastating effects on the fetus. The sonographic intracranial findings consistent with intrauterine infections are the calcifications around the ventricles and ventriculomegaly. (T.W Sadler et al, 2012)

2.3.4.3.6 Skeletal System:

2.3.4.3.6.1 Malformation of the Vertebrae:

Scoliosis: lateral curving of the spine.

Also, number of vertebrae is more or less than the normal.

Kipple-fiel Sequence: The cervical vertebrae are fused causing reduced mobility and short neck. (Samuel Webster et al, 2016)

Spina Bifida (cleft vertebrae): One of serious vertebral defects result of imperfect fusion or nonunion of the vertebral arches. And this may only the bony vertebral arches, leaving the spinal cord intact and known as spina bifida occulta. Open neural tube defects are characterized by exposure of the meninges and neural tissue to the amniotic fluid. Although it had previously been assumed that the spinal cord was intrinsically defective, it is becoming more evident that secondary

destruction of the spinal tissue occurs due to exposure to the amniotic fluid or direct trauma from fetal movements. (Samuel Webster et al, 2016)

Spina Bifida Cystica: Sever spina bifida in which the neural tube fails to close, vertebral arches fail to form, and neural tissue to exposed. (Samuel Webster et al, 2016)

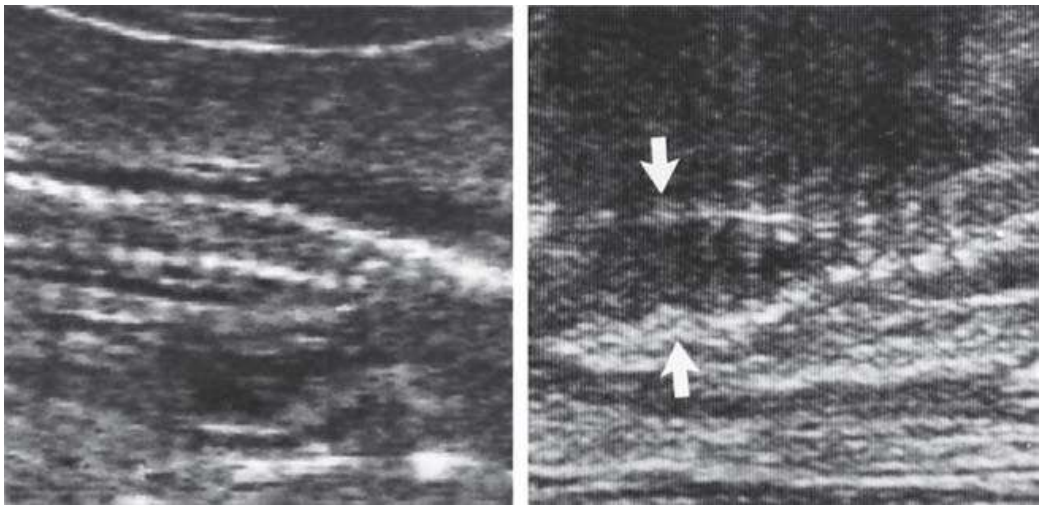


Figure (2.17) LT: normal vertebral RT: vertebra with spina bifida (T. W. Sadler et al, 2012)

2.3.4.3.6.2 Malformation of Rib:

Extra Rib: Occasionally extra rib may form, usually in the lumber and cervical region. (Samuel Webster et al, 2016)

2.3.4.3.6.3 Defects of Sternum:

Cleft Sternum: Is very rare and may be complete or located at either end of sternum. It occurs when the sternal band fail to grow together in the midline. (Samuel Webster et al, 2016)

Hypoplastic Ossification centers and premature fusion of sternal segments also occur particularly in infant with congenital heart defects (20-50%). (Samuel Webster et al, 2016)

Multiple Mandibular Ossification Centers: Occur in (6-20%) of all children but are especially common in those with Down Syndrome. (Samuel Webster et al, 2016)

Pectus Excavatum: Is the term for a depressed sternum that is sunken posteriorly. (Samuel Webster et al, 2016)

Pectus Carinatum: It is referring to a flatting of the chest bilaterally with an anterior projecting sternum. Both defects may result from abnormalities of ventral body wall closure or formation of the costal cartilages and sternum. (Samuel Webster et al, 2016)

2.3.4.3.7 Cardiovascular System:

2.3.4.3.7.1 Heart Defect: Heart and vascular abnormalities make up the largest category human birth defect and are present in 1% of live born infant. The incidence among stillborn is 10 times as high. It is estimated that 12% of babies with heart defects have chromosomal abnormality and, conversely that 33% of babies with chromosomal abnormalities have heart defects. In some condition, such as trisomy 18, the incidence of the heart defect 100%. Approximately 2% of the heart defects are caused by a complex inter play between genetic and enviroment influences (multifactorial causes). Classic examples of cardiovascular teratogens include rubella virus, thaliclomide. Others include Accutone (RA), alcohol, maternal disease, such as insulin-dependent diabetes, have also linked to cardiac defect. (Kevin Coward et al, 2013)

Hypertrophic Cardiomegaly: The disease is inherited as an autosomal dominate. It caused sudden death. It results from disruption in organization of cardiac muscles cells (myocardial disarray, which may adversely affect cardiac output and/or conduction). (Kevin Coward et al, 2013)

Ventricular Inversion: Is a defect in which the morphologic left ventricular is on the right and connects to the right atrium through a mitral valve. The morphologic right ventricle is on the left side and connects to the left atrium through the tricuspid valv. The defect sometimes called L transposition of great arteries

because the pulmonary artery exits the morphologic left ventricle. However, the arteries are in their normal position, but the ventricles are reversed. (Kevin Coward et al, 2013)

Atrial Septal Defect (ASD): Is a congenital heart abnormality with an incidence of 6.4/10,000 births and with 2:1 prevalence in female to male infants. The most significant defects is the:

Ostium Secundum: It is a defect characterized by a large opening between the left and right atria. It may cause by the excessive cell death and resorption of the septum primum, or by the inadequate development of the septum secundum. (Kevin Coward et al, 2013)

Cor Trilocular Biventricular: It is complete absence of the atrial septum. It is always associated with serious elsewhere in the heart. (Kevin Coward et al, 2013)

Ostium Primum Defect: Is usually combined with a cleft in the anterior leaflet of the tricuspid valv. (Kevin Coward et al, 2013)

Tricuspid Atresia: It is involving obliteration of the right atrioventricular orifice, is characterized valves. It is always associated with patency of the oval formation, VSD, under development of the right ventricle, and hypertrophy of the left ventricle. (Kevin Coward et al, 2013)

Ebstein Anomaly: Is a condition where the tricuspid valv is displaced toward the apex of the right ventricle. The valv leaflets are abnormally positioned and the anterior one is usually be enlarged. As result there is hypertrophy of the right atrium with a small right ventricle. (Kevin Coward et al, 2013)

Ventricular Septal Defect (VSDs): Involving the membranous or muscular portion of the septum. It is the most common cardiac defect occurs in 12/10,000 births. (Kevin Coward et al, 2013)

Tetralogy Of Fallot: The most frequently occurring abnormality of the conotruncal region, is due to an unequal division of the conus resulting from anterior displacement of the conotruncal septum. Displacement of the septum produced four cardiovascular alteration: narrow right ventricular out flow region, pulmonary fundibular stenosis, a large defect of the interventricular septum, an

overriding aorta that arises directly above the defect, and hypertrophy of the right ventricular wall because of the high pressure on the right side. (Kevin Coward et al, 2013)

Persistent (common) Truncus Arteriosus: It results when the conotruncal ridges fail to form, so that no division of the out-flow tract occurs. In such case, which occurs in 0.8 of 10,000 birth the pulmonary artery arises some distance above the origin of the undivided trunk. (Kevin Coward et al, 2013)

Transposition of The Great Vessels: Occurs when the conotruncal septum fails to follow its normal spiral course and runs straight down. As a consequence, the aorta originates from the right ventricle, and the pulmonary artery originates from the left ventricle. This condition, which occurs in 4.8 of 10,000 birth, sometime is associated with a defect in the membranous part of the interventricular septum. It is usually accompanied by an open ductus arteriosus. (Kevin Coward et al, 2013)

Di George Sequence: It is characterized by a pattern of malformations abnormal neural crest development. These children have facial defect, thymus hypoplasia, parathyroid dysfunction and cardiac abnormalities involving the outflow tract, such as persistent truncus arteriosus and tetralogy of fallot. Craniofacial malformations are often associated with heart defect because neural crest cells play important roles in the development of the both the face and heart. (Kevin Coward et al, 2013)

Valvular Stenosis: The valvular stenosis of pulmonary artery or aorta occurs when the semilunar valves are fused for a variable distance. The incidence of the abnormality is similar for both regions, begin approximately 3 to 4 of 10,000 birth. In case of pulmonary artery valvular stenosis: the trunk of the pulmonary is narrow or even atretic. The patent oval foramen then forms the only one outlet for blood from the right side of the heart. The ductus arteriosus, always patent, is the only access route to pulmonary circulation. In aortic valvular stenosis: fusion of the thickened valves may be complete so that only a pinhole opening remains. The size of the aorta itself is usually normal. (Kevin Coward et al, 2013)

Aortic Valvular Atresia: The aorta, left ventricle, and left atrium are markedly under developed. The abnormality is usually accompanied by an open ductus arteriosus, which delivers blood into the aorta. (Kevin Coward et al, 2013)

Actopia Cardis: it is rare anomaly in which the heart lies on the surface of the chest. It is caused by failure of the embryo to close the ventral body wall. (Kevin Coward et al, 2013)

2.3.4.3.7.2 Venous System Defect:

A Double Inferior Vena Cava: Occurs when the left sacrocardinal vein fails to lose its connection with the subcardinal vein. The left common iliac vein may or may not be present, but the left gonadal vein remains as in the normal condition. (Kevin Coward et al, 2013)

Absence of the Inferior Vena Cava: Arises when the right subcardinal vein fails to make its connection with the liver and shunt its blood directly into the right supracardinal vein. Hence, the blood stream from caudal part of the body arches the heart by way of the a zygos vein and superior vena cava. The hepatic vein enters into the right atrium at the site of the inferior vena cava. Usually, it is associated with other heart malformation. (Kevin Coward et al, 2013)

Left Superior Vena Cava: Is caused by persistence of the left anterior cardinal vein and obliteration of the common cardinal and proximal part of the anterior cardinal veins on the right, in such case, blood from the right is channeled toward the left by the left way of the brachiocephalic vein. The left superior vena cava drains into the right atrium by way of the left sinus horn, that is the coronary sinus. (Kevin Coward et al,2013)

Double Superior Vena Cava: Is characterized by the persistence of the left anterior cardinal vein and failure of the left brachiocephalic vein to form. The persistent left anterior cardinal vein, the left superior vena cava, drains into the right atrium by way of the coronary sinus. (Kevin Coward et al, 2013)

2.3.4.3.7.3 Atrial System Defect:

Patent Ductus Arteriosus: One of the most frequent occurring abnormalities of the great vessels (8/10,000) birth especially in premature infant, either may be an isolated abnormality or may be accompany with other heart defect. (Kevin Coward et al, 2013)

Coarctation Of the Aorta: Which occurs in 3.2 of 10,000 birth, the aortic lumen below the region of the left subclavian artery is significantly narrowed. Since the constriction may be above or below the entrance of the ductus arteriosus, two types (preductal or postductal) may be distinguished. The cause of narrowing is an abnormality in the media of the aorta, followed by intima proliferations. In the preductal type, the ductus arteriosis persists, where as in the postductal type, which is more common, this channel is usually obliterated. (Kevin Coward et al, 2013)

Abnormal Origin of The Right Subclavian Artery: Occurs when the artery formed by the distal portion of the right dorsal aorta and the seven intersegmental arteries. The right fourth aortic arch and the proximal part of the right dorsal aorta obliterated with shortening of the aorta between the left common carotid and left subclavian artery finally settle just below that of the left subclavian. (Kevin Coward et al, 2013)

Double Aortic Arch: The right dorsal aorta persists between the origin of the seventh intersegment artery and its junction with the left dorsal aorta. (Kevin Coward et al, 2013)

2.3.4.3.8 Respiratory System Defect:

Can occurs with or without tracheoesophageal fistula (TEFs). These defects occur in approximately 1/3000 birth, and 90% result in the upper portion of the esophagus ending in blind pouch and the lower segment forming a fistula with the trachea. (T. W. Sadler et al, 2012)

Isolated Esophageal Atresia & H-type TEF: can occur without esophageal arteries each account 4% of these defects. Other variations each account for approximately 1% of these defects. These abnormalities are associated with other

birth defects, including cardiac abnormalities, which occur in 33% of these cases. In this regard, TEFs are a component of VACTER association (Vertebral anomalies, Anal atresia, Esophageal atresia, Renal anomalies, and limb defects), a collection of defects of unknown causation, but occurring more frequently than predicated chance a lone. A complication of some TEFs is polyhydramnios, since in some types of TEF, amniotic fluid, when swallowed does not pass to stomach and intestines. Also, gastric content and/or amniotic fluid at birth may enter the trachea through a fistula, causing pneumonitis and pneumonia. (T.W. Sadler et al, 2012)

Ectopic lungs lobes: Arising from the trachea or esophagus. It is believed that these lobes are formed additional respiratory buds of the forgut that developed independent of the main respiratory system. (T. W. Sadler et al, 2012)

Congenital lung Cyst: Formed by dilation of the terminal or larger bronchi. These cysts may be small and multiple, giving the lung a honey comb appearance on radiograph, or may be restricted to one or more larger ones. Cystic structures of the lung usually drain poorly and frequently cause chronic infections. (T. W. Sadler et al, 2012)

2.3.4.3.9 Digestive System Defect:

2.3.4.3.9.1 Esophagus:

Esophageal Atresia: Occurs with or without tracheoesophageal fistula. Result either from spontaneous posterior deviation of trachea- esophageal septum or from some mechanical factors pushing the dorsal wall of the foregut anteriorly. (Bruce M. Carlson 2014)

Esophageal stenosis: Usually in the lower third. Stenosis may be caused by incomplete recanalization, vascular abnormalities, or accident that promise blood flow. Occasionally, the esophagus fails to lengthen suffiently, and the stomach is pulled up into the esophageal hiatus through the diaphragm. The result is a congenital hiatal hernia. (Bruce M. Carlson 2014)

2.3.4.3.9.2 Stomach Abnormalities:

Pyloric Stenosis: Occurs when the circular and, to a lesser degree, the longitudinal musculature of the stomach in the region of the pylorus hypertrophies. One of the most common abnormalities of the stomach in infant, pyloric stenosis was previously believed to develop only during fetal life, despite the fact that most cases present 3 to 5 days after birth. Pyloric stenosis characterized by an extreme narrowing of the pyloric lumen, and the passage of the food is obstructed, resulting in severe projectile vomiting. In a few cases, the pylorus is atretic. Other malformations of the stomach such as duplications and prepyloric septum are rare. (Bruce M. Carlson, 2014)

2.3.4.3.9.3 Liver and Gall Bladder Defects:

Variations in liver lobulation are common but not clinically significant.

Accessory Hepatic Ducts and Duplication of the Gall Bladder: Are common and usually important, under pathological condition. In some cases, the duct, which pass through a solid phase, their development fails to recanlize. (Bruce M. Carlson, 2014)

Extrahepatic Biliary Atresia: Occurs in 1/15000 live birth. Among patient with extrahepatic biliary atresia, 15% to 20% have patent proximal ducts a correctable defect, but the reminder usually dies unless they receive a liver transplant. (Bruce M. Carlson, 2014)

Intrahepatic Biliary Duct Atresia: This a rare abnormality (1/100,000 live birth) may be caused by fetal infections. It may be lethal but usually runs an extended course. .(Kevin Coward et al, 2013)

2.3.4.3.9.4 Pancreatic Defect: The ventral pancreatic bud consist of two component that normally fuse and rotate around the duodenum so that they come to lie below dorsal pancreatic duct bud. (Bruce M. Carlson, 2014)

Accessory Pancreatic Tissue: May be anywhere from the distal end of the esophagus to the tip of the primary intestinal loop. Most frequently, it lies in the mucosa of stomach and in Meckle's diverticulum, where it may show all of the histological characteristic of the pancreas itself. (Bruce M. Carlson, 2014)

2.3.4.3.10 Mesenteries Defects:

Normally the ascending colon except for its most caudal part (approximately 1 inch) fuse to posterior abdominal wall and is covered by peritoneum on its anterior surface and sides. Persistence of a portion of mesentery of ascending colon fails to fuse with posterior body wall. Such a long mesentery allows abnormal movements of the gut or even volvulus of the cecum and colon. Similarly, incomplete fusion of the mesentery with posterior body wall may give rise to retrocolic pockets behind the ascending mesocolon. (W.T Sadler et al, 2012)

2.3.4.3.11 Body Wall Defect:

Omphalocele: Involves herniation of abdominal viscera through an enlarged umblical ring. The viscera, which may be include liver, small and large intestine, stomach, spleen and GB are covered by amnion. The origin of the defect is a failure of the bowel to return to the body cavity from its physiological herniation during 6^{th} to 10^{th} weeks. Omphalocele occurs in 2.5/10,000 birth and is associated with a high rate mortality (25%) and severe malformations, such as cardiac anomalies (50%) and neural tube defect (40%). Approximately 15% of live born infant with omphalocele have chromosomal abnormalities. (W.T Sadler et al, 2012)

Gastroschisis: In the term applied to protrusion of abdominal contents through the body wall directly into the amniotic cavity. It occurs lateral to the umbilicus usually on the right, and the defect is most likely due to abnormal closure of the body wall around the connecting stalk. Viscera are not covered by peritoneum or amnion, and the bowel may be damage by exposure to amnion fluid. Gastroschisis occurs in 1/10,000 birth but is increasing in frequency, especially among young

women (less than 20 years old). The reason for this increase and why the defect is more prevalent in babies born to younger women is not known. Unlike omphalocele, gastroschisis is not associated with chromosomal abnormalities or other severe defects, so the survival rate is excellent. Volvulus (rotation of the bowel) resulting in a compromised blood supply may, however, kill large regions of the intestine and lead to fetal. (W.T Sadler et al, 2012)

Vitelline Duct Abnormalities: In 2% to 4% of people, a small portion of the vitelline duct persists, forming an out pocketing of the ileum, Meckle's diverticulum or ileal diverticulum in the adult, this diverticulum, approximately 40 to 60cm from the ileocecal valv on the antimesentric border of the ileum does not usually cause any symptoms. However, when it contains heterotopic pancreatic tissue or gastric mucosa, it may undergo ulceration, bleeding, or even perforation. Sometimes, both ends of the vitelline duct transform into fibrous cords, and the middle portion forms a large cyst, an enterocystoma or a vitlline cyst. Since the fibrous cords traverse the peritoneal cavity, intestinal loops may twist around the fibrous strands and become obstructed, causing strangulation nor volvulus. In another variation, the vitelline duct remains patent over its entire length, forming a direct communication between the umbilicus and intestinal tract. This abnormality is known as umblical fistula, or vitelline fistula. A fecal discharge may then be found at the umbilicus. (W.T Sadler et al, 2012)

Gut Rotation Defect: Malrotation of the intestinal loop may result in twisting of intestine (volvulus) and comprise of the blood supply. Normally, the primary intestinal loop rotates 270 degree counter clockwise. Occasionally, however, rotation amount to 90 degree only. When this occurs, the colon and cecum are the first portions of the gut to turn from the umblical cord, and they settle on the left side of the abdominal cavity, the later returning loops, then move more and more to the right, resulting in a left-sided colon. (Kevin Coward et al, 2013)

Reversed Colon of the Intestine Loop: May occur when the primary loop rotates 90 degree clockwise. In this abnormality the transvers colon passes behind the

duodenum and lies behind the superior mesenteric artery. (Kevin Coward et al, 2013)

Duplication of The Intestinal Loops and Cyst: May occur anywhere along the length of the gut tube. They are most frequently found in the region of the ileum, where they may be varying from along segment to a small diverticulum. Symptoms usually occur early in life and 33% are associated with other defects, such as intestinal atresia, imperforate anus, gastroschisis, and omphalocele. Their origin is unknown, although they may result from abnormal proliferations of gut parenchyma. (Kevin Coward et al, 2013)

Gut Atresia and Stenosis: May occur anywhere along the duodenum, fewest in colon and equal numbers occur in jejunum and ileum (1\1500 birth effects). Atresia in the upper duodenum are probably due to a lake of recanalization from the distal portion of the duodenum caudally, however, stenosis and atresia were thought to be caused by vascular (accidents) that result in compromised blood flow and tissue necrosis in a section of the gut resulting in the defect. It was suggested that these accidents could be caused by malrotation, volvulus, gastroschisis, omphalocele, and other factors. However, new evidence suggests that problems with gut differentiation can also cause these defects. In 50% of cases, a region of the bowel is lost and in 20%, a fibrous cord remains. In another 20%, there is a narrowing, with a thin diaphragm separating the larger and smaller pieces. Stenosis and multiple atresias a count for remaining 10% of these defects, with frequency of 5% each. (W.T Sadler et al, 2012)

Apple Peel Atresia: A counts for 10%of atresia. The atresia is in the proximal jejunum, and the intestine is short, with the portion distal to the lesion coiled around a mesenteric remnant effects of the atresia on newborns depend on the amount of the bowel that has been damaged and its location. Some babies extensive gut involvement has low birth weight and other abnormalities. (W.T Sadler et al, 2012)

2.3.4.3.12 Hindgut Abnormalities:

Rectourethral and Rectovaginal Fistula: Which occur in 1/15.000 live birth, may be caused by abnormalities in formation of the cloca and/or the urorectal septum. For example, if the cloaca is too small, or if the urorectal septum does not extend far enough caudally, then opening of the hindgut shifts anteriorly leading to the opening of the hindgut into the urethral or vagina. (W.T Sadler et al, 2012)

Rectoanal Fistula and Atresia: Vary in severity and may leave a narrow tube or fibrous remnant connected to the perineal surface these defects are probably due to misexpression of the genes during epithelial-mesenchymal signaling. (W.T Sadler et al, 2012)

Imperforate Anus: Occurs when the anal membrane fails to breakdown. (W.T Sadler et al, 2012)

Congenital Megacolon: It due to the absence of the parasymypathic ganglia in the bowl wall (a ganglionic megacolon or Hirschsprung disease). These ganglia are derived from neural crest cells that migrate from the neural fold to the wall of the bowel. Mutation in the RET gene, a tyrosine Kinase receptor involved in crest cell migration, can result in congenital megacolon. In most cases, the rectum is involved, and in 80%, the defect extends to the midpoint of the sigmoid. In only 10% to 20 %are the transverse and right-side colonic segments involved, and 3%, the entire colon is affected**.** (W.T Sadler et al, 2012)

2.3.4.3.13 Urogenital Defects:

WiIim's Tumor: Is a cancer of the kidneys that usually affects children by 5 year. Wilim's tumor is due to the mutations in the WTI gene 0n 11p13, and it may be associated with other. (W.T Sadler et al, 2012)

Denys-Drash Syndrome: Consist of renal failure, ambiguous genitalia, and Wilim's tumor. (W.T Sadler et al, 2012)

Renal Dysplasia & Agenesis: Are a spectrum of severe malformation that represent the primarly disease requiring dialysis and transplantation in the first years of life. (W.T Sadler et al, 2012)

Multicystic Dysplastic kidney: There are numerous ducts are surrounded by undifferentiated cells. Nephrons fail to develop, and the ureteric bud fails to branch, so that the collecting ducts never form in some cases, these defects cause involution of the kidneys and renal agenesis. Renal agenesis may also arise if the interaction between the metanephric mesoderm and uretric bud fails to occur. Bilateral renal agenesis, which occurs in 1/10,000 births, result in renal failure. The baby presents with potter sequence, characterized by anuria, oligohydramnios, and hypoplastic lungs secondary to the oligohydramnios. In 85% of cases, other severe defects, including absence or abnormalities of the vagina and ureter, vas deferencs, and seminal vesicles, accompany this condition. Common associated defect in other systems include cardiac anomalies, tracheal and duodenal atresia, cleft lip and palate, and brain abnormalities. Because of the oligohydramnios, the uterine cavity is compressed resulting in a characteristic appearance of the fetus, including a flattened face (potter faces) and club feet. (W.T Sadler et al, 2012)

Congenital Polycystic Kidney Disease: In congenital polycystic kidney disease numerous cyst form. It may be inherited as an autosomal recessive or autosomal dominant disorder or may cause by other factors. (W.T Sadler et al, 2012)

Autosomal Recessive Polycystic: 0ccures in 1/5000 births, is progressive disorder, in which cysts from collecting ducts. The kidney become very large, and renal failure occurs in infancy or childhood. (W.T Sadler et al, 2012)

Autosomal Dominant Poly Cystic Kidney Disease (ADPKD): Cyst form from all segments of the nephron and usually do not cause renal failure until adulthood. The autosomal dominate disease is more common (1/500-1/1000) births, but less progressive than the autosomal receive disease. Both types of disease are linked to mutations in genes that encode proteins localized in cilia and that are important for ciliary function. (W.T Sadler et al, 2012)

Ciliopathies: Due to mutation in cilia related proteins. These disorders include:

- Bardet-Biedal Syndrome: which characterized by renal cysts, obesity, intellectual disability, and limbs defects.
- Meckel Gruber Syndrome: characterized by renal cysts hydrocephalus, mirophalmia, cleftpalate, absence of the olfactory tract, and polydactyly.

Duplication of the Ureter: Result from early splitting of the ureteric bud. Splitting may be partial or complete, and metanephric tissue may be divided into two parts, each with into two parts, each with its own renal pelvis and ureter. (W.T Sadler et al, 2012)

Abnormal Location of the Kidney: consist of

- Pelvic kidney: During their ascent, the kidneys pass through the arterial fork formed by the umblical arteries, but occasionally, one of them fails to do so. Remaining in the pelvis close to the iliac artery.
- Horseshoe kidney: some times, the kidneys are pushed so close together during their passenger through the aterial fork, that the lower poles fuse it is usually at the level of the lower lumber vertebra. (W.T Sadler et al, 2012)

Accessory Renal Arteries: Are common, they derive from the persistence of embryonic vessels that formed during ascent of the kidney. These arteries usually arise from the aorta and enter the superior or inferior poles of the kidneys. (W.T Sadler et al, 2012)

Bladder Defects: consist of

- Exstrophy of the Bladder: Is a ventral body wall defect in which the bladder mucosa is exposed.
- Epispadias: Is a constant feature, and open urinary tract extends along the lateral body wall folds to close in the midline in the pelvic region. This anomaly is rare, occurring in 2/100,000 live birth.

- Exstrophy of Cloaca: Is more severe ventral body wall defect in which progression and closure of the lateral body wall fold are more disrupted to a great degree than is observed in bladder extrophy. In addition to the closure defect, normal development the urorectal septum is altered, such that anal canal malformations and imperforate anus occur. Furthermore, since the body folds do not fuse, the genital swelling are widely spaced resulting in defects in the external genitalia occurance of the defect is rare (1/30,000). (W.T Sadler et al, 2012)

Uterine and Vaginal Defects: Result from lake of fusion of the paramesonephric ducts in a local area or throughout their normal line of fusion. In its extreme form the uterus is entirely double (uterus didelphys), in the last severe form, it only slightly indented in the middle (uterus arcuatus), also uterus may have two horns entering the vagina. (W.T Sadler et al, 2012)

Defect in the Male Genitalia:

- Hypospadias: Fusion of the urethral fold is incomplete, and abnormal opening of the urethra occur along the inferior aspect of the penis, usually near the glans, along the shaft, or near the base of penis. In rare cases, the urethral meatus extends along the scrotal when fusion of the urethral folds fails entirely, a wide sagittal slit is found along the entire length of the penis and the scrotal. The two scrotal swelling then closely resemble the labia major. The incidence hypospadias is 3 to 5/1000 births, and this rate represents a doubling over the past 15 to 20 years, reasons for the increase are not known, but one hypothesis suggests that it could be result of arise in environmental estrogens (endocrine disrptors).
- Epispadias: Is a rare abnormality (1/30,000 birth) in which the urethral meatus is found on the dorsum of the penis. Although epispadias may occur as an isolated defect, it is most often associated with exstrophy of the bladder and abnormal closure of the ventral body wall.

- Micropenis: Occur when there is insuffient androgen simulation for growth of the external gentalia. Micropenis is usually caused by primary dysfunction.
- Bifid Penis or A Double Penis: May occur if the genital tubercle splits.

Hernias & Cryptorchidism:

- Congenital Indirect Inguinal Hernia: The connection between the abdominal cavity and the processus vaginalis in the scrotal sac normally closes in the first year after birth.
- Hydrocele of The Testes And/or Spermatic Cord: Sometimes, obliteration of the passageway is irregular, leaving small cysts along its course. Later, these cysts may secrete fluid.

2.4 Ultrasound Physics:

Ultrasound has been used for diagnostic purpose in medicine since late 1940s, but the history of ultrasound dates back to ancient Greece. (Nimrod M. Tole, 2005)

2.4.1 Principles of Ultrasound: Sound waves are emitted by piezoelectric material, most often synthetic ceramic material (lead zirconate titanate [PZT], that is contained in ultrasound transducers. When a rapidly alternating electrical voltage is applied to piezoelectric material, the material experiences corresponding oscillations in mechanical strain. As material expands and contracts rapidly, vibrations in the adjacent material are produced and sound waves are generated. Mechanical properties of piezoelectric material determine the range of sound wave frequencies that are produced. Sound waves propagate through media by creating compressions and rarefactions of spacing between molecules. This process of generating mechanical strain from the application of an electrical signal to piezoelectric material is known as the reverse piezoelectric effect. The opposite process, or generation of an electrical signal from mechanical strain of piezoelectric material, is known as the direct piezoelectric effect. Frequency and

Wavelength: By definition, “ultrasound” refers to sound waves at a frequency above the normal human audible range (>20 kHz). Frequencies used in ultrasonography range from 2 to 18 MHz. Frequency **(*f*)** is inversely proportional to wavelength **(*λ*)** and varies according to the specific velocity of sound in a given tissue **(*c*)** according to the formula**:** (Nimrod M. Tole, 2005)

$$\lambda = c/f$$

Two important considerations in ultrasonography are the penetration depth and resolution, or sharpness, of the image; the latter is generally measured by the wavelength used. For example, when wavelengths of 1 mm are used, the image appears blurry when examined at scales smaller than 1mm. Ultrasound waves with shorter wavelengths have higher frequency and produce higher-resolution images, but penetrate to shallower depths. Conversely, ultrasound waves with longer wavelengths have lower frequency and produce lower-resolution images, but penetrate deeper. The relationship between frequency, resolution, and penetration for a typical biologic material is demonstrated in maximizing axial resolution while maintaining adequate penetration is a key consideration when choosing an appropriate transducer frequency. Higher frequencies are used in linear-array transducers to visualize superficial structures, such as vasculature and peripheral nerves. Lower frequencies are used in curvilinear and phased-array transducers to visualize deeper structures in the thorax, abdomen and pelvis. (Nimrod M. Tole, 2005)

2.4.2 Power and Intensity: Average power is the total energy incident on a tissue in a specified time (W). Intensity is the concentration of power per unit area (W/cm2), and intensity represents the “strength” of the sound wave. The intensity of ultrasound waves determines how much heat is generated in tissues. (Nimrod M. Tole, 2005)

2.4.3 Type of Resolution:

Resolution: Image resolution is divided into axial, lateral, elevational, and temporal components. (Nimrod M. Tole, 2005)

- Axial Resolution: It is the ability to differentiate two objects along the axis of the ultrasound beam. It depends on transducer frequency.
- Lateral Resolution (horizontal resolution): It is the ability to differentiate two objects perpendicular to the ultrasound beam and is dependent on the width of the beam at a given depth.
- Elevational Resolution: It is a fixed property of the transducer that refers to the ability to resolve objects within the height, or thickness, of the ultrasound beam.
- Temporal Resolution: It is refers to the clarity, or resolution, of moving structures. (Nimrod M. Tole, 2005)

2.4.4 Generation of Ultrasound Images: Ultrasound images are generated by sound waves reflected and scattered back to the transducer. Transducers receive and record the intensity of returning sound waves. Specifically, mechanical deformation of the transducer's piezoelectric material generates an electrical impulse proportional to the amplitude of these returning sound waves. Electrical impulses cumulatively generate a map of gray-scale points seen as an ultrasound image. Depth of structures along the axis of the ultrasound beam is determined by the time delay for echoes to return to the transducer. The process of emitting and receiving sound waves is repeated sequentially by the transducer, resulting in a dynamic picture. Reflection and propagation of sound waves through tissues depend on two important parameters: acoustic impedance and attenuation: (Peter Hoskins, 2010)

- Acoustic Impedance: Is the resistance to propagation of sound waves through tissues and is a fixed property of tissues. Greater differences in acoustic impedance lead to greater reflection of sound waves. (Peter Hoskins, 2010)

- Attenuation: As sound waves travel through tissues, energy is lost, and this loss of energy is called attenuation. Attenuation is due to absorption, deflection, and divergence of sound waves and is dependent on the attenuation coefficient of tissues, frequency of sound waves, and distance traveled by sound waves. (Peter Hoskins, 2010)

2.4.5 Modes of Ultrasound Image:

2.4.5.1Two-Dimensional Mode: Two-dimensional (2D) mode is the default mode of most ultrasound machines, and the majority of bedside diagnostic ultrasound imaging is performed in 2D mode. This mode is also called B-mode, for brightness, because echogenicity, or brightness, of observed structures depends on the intensity of reflected signals. Structures that transmit all sound waves without reflection are called anechoic and appear black on ultrasound. Most fluid-filled structures appear anechoic. Structures that reflect some sound but less than surrounding structures appear hypoechoic, whereas structures that reflect sound waves similar to surrounding structures appear isoechoic. Hyperechoic structures reflect most sound waves and appear bright white on ultrasound. (Peter Hoskins, 2010)

2.4.5.2 M-Mode: M-mode, or motion mode, is an older mode of imaging but is still frequently used today to analyze movement of structures over time. After a 2D image is acquired, M-mode imaging is applied along a single line within the 2D image. For example, M-mode is used to measure the size of cardiac chambers or movement of cardiac valves throughout the cardiac cycle.(Peter Hoskins, 2010)

2.4.5.3 Doppler Imaging: The Doppler effect is a shift in frequency of sound waves due to relative motion between the source and observer. The primary source of sound waves is the transducer, and the same transducer is the observer for returning echoes. Movement of tissues, such as blood flow, produces a shift in frequency of returning sound waves. The change in frequency between the emitted

and received sound waves is called Doppler shift. Variables that determine the amount of Doppler shift are frequency of ultrasound beam, **v**elocity of blood flow, **a**ngle of insonation (the angle between the ultrasound beam and direction of the measured flow). No Doppler shift can be measured when the ultrasound beam is perpendicular to the direction of blood flow.(Peter Hoskins, 2010)

2.4.5.4 Spectral Doppler: Doppler effect may be represented graphically using velocity (*y*-axis) plotted over time (*x*-axis) in a display method called spectral Doppler. Spectral Doppler permits quantitative assessment of velocities and is divided into two types: pulsed wave and continuous wave. Pulsed-wave Doppler refers to the emission of sound waves in pulses that allows measurement of Doppler shift at certain depths. After a pulsed signal is sent into tissues, the transducer must await the returning echo before emitting another pulse.(Peter Hoskins, 2010)

2.4.5.5 Color Flow Doppler: Color flow Doppler images display color-coded maps representing Doppler shifts that are superimposed on 2D ultrasound images. Color flow Doppler relies on the same principles as pulsed-wave Doppler, but shorter pulses are obtained from multiple small areas to build a color-coded map. When velocities exceed the Nyquists limit, pixels appear as a mosaic color pattern (blue, red, and white) as the direction of flow cannot be reliably ascertained.(Peter Hoskins, 2010)

2.4.5.6 Power Doppler: A newer Doppler technique, called power Doppler, has unique characteristics. Power Doppler assesses echo signals similar to color flow Doppler, but power Doppler analyzes only the amplitude of returning echoes. Thus, power Doppler is superimposed on a 2-D image, and the levels of brightness correlate with magnitudes of flow. (Peter Hoskins, 2010)

2.4.6 Transducer Construction: Ultrasound transducers are designed for optimal transmission and reception of sound waves. An electrical shield lines the transducer case to prevent external electrical interference from distorting sound wave transmission. A thin acoustic insulator dampens vibrations from the case to

piezoelectric elements and prevents transmission of spurious electric current to the machine's computer processor. At the tip of the transducer, a thin matching layer improves efficiency of sound wave transmission from piezoelectric elements to skin and deeper structures. Backing material is an essential component of transducers. Backing material is fixed behind the layer of 1piezoelectric elements to dampen ongoing vibrations of elements. Sound energy is absorbed by backing material when elements are generating and receiving sound waves. (Peter Hoskins, 2010)

2.5 Previous Study:

2.5.1 Diabetes Mellitus:

2.5.1.1 Definition of DM:

WHO/IDF consultation 2016 in a study (Definition and diagnosis of diabet1es mellitus and intermediate hyperglycemia) report that **s**ince 1965 the World Health Organization (WHO) has published guidelines for the definition, diagnosis and classification of diabetes. These were last reviewed in 1998 and were published as the guidelines for the Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Since then more information relevant to the diagnosis of diabetes has become available. In November 2005 a joint WHO and International Diabetes Federation (IDF) Technical Advisory Group met in Geneva to review and update the current WHO guidelines. After consideration of available data and recent recommendations made by other organizations, the Group made the following recommendations: The current WHO diagnostic criteria for diabetes should be maintained:

Fasting plasma glucose $\geq$ 7.0mmol/l (126mg/dl)

2–h plasma glucose $\geq$ 11.1mmol/l (200mg/dl).

Despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased

premature mortality and increased risk of micro vascular and cardiovascular complications. The fasting plasma glucose cut-point for Impaired Fasting Glucose (IFG) should remain at 6.1mmol/l. This decision was based on concerns about the significant increase in IFG prevalence which would occur with lowering the cut-point and the impact on individuals and health systems. There is a lack of evidence of any benefit in terms of reducing adverse outcomes or progression to diabetes and people identified by a lower cut-point eg 5.6mmol/l (100mg/dl) have a more favorable cardiovascular risk profile and only half the risk of developing diabetes compared with those above the current WHO cut point. Lowering the cut-point would increase the proportion of people with IGT who also have IFG but decreases the proportion of people with IFG who also have IGT. Consideration should be given to replacing this category of intermediate hyperglycemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which includes a measure of glucose as a continuous variable.

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy, regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes. Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes at their initial prenatal visit, using standard diagnostic criteria. Women diagnosed with diabetes in the first trimester should be classified as having preexisting pregestational diabetes (type 2 diabetes or, very rarely, type 1 diabetes). GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes.

2.5.1.2 Incidence of DM:

Carlos Antonio et al, in their study (Adverse pregnancy outcomes in women with diabetes 2012) said 2 to 17.8% of women develop gestational diabetes, depending on the diagnostic criteria used and the studied population; gestational diabetes represents a very strong predictor for the development of permanent diabetes later in life . Besides gestational diabetes, pregnancy can also occur in women with preexisting diabetes. A significant increase in preexisting diabetes during pregnancy has been observed in the USA between 1999 and 2005, rising from 10% to 21%.

2.5.1.3 Classification of DM with pregnancy: Stevie N. Bennett et al, 2016 in their study Assessing White's Classification of Pregestational Diabetes in a Contemporary Diabetic Population. The White's classification was developed by Priscilla White in 1949 to estimate the risks of "perinatal wastage" in pregnancies complicated by diabetes.[1] She concluded that pregnancy complications could be predicted by maternal factors such as disease duration, age of onset, and the presence or absence of vascular diseases such as "transitory" hypertension, retinopathy, nephropathy, or heart disease. In the 1980 revision, the classification system was revised to upstage those with chronic hypertension to class D regardless of their age at diagnosis or duration of disease.

There are 2 classes of gestational diabetes (diabetes which began during pregnancy):

Class A_1: gestational diabetes; diet controlled,

Class A_2: gestational diabetes; medication controlled

The second group of diabetes which existed before pregnancy can be split up into these classes:

Class A: Diagnosis of diabetes made on a glucose tolerance test, which deviates but slightly from the normal

Class B: Duration less than 10 y and Onset age 20 y or older and No vascular disease

Class C: Duration 10–19 y or Onset 10–19 y of age or Minimal vascular disease (eg, retinal arteriosclerosis or calcified leg vessels)

Class D: Duration 20 y or longer or Onset younger than 10 y of age or More evidence of vascular disease, eg, retinitis, transitory albuminuria, or transitory hypertension

Class E: Calcified pelvic arteries on X-ray

Class F: Nephritis

An early age of onset or long-standing disease comes with greater risks, hence the first three subtypes.

2.2.1.4 Comorbidities:

Debra Manzell et al, September 2018 in their study: How Comorbid Conditions Can Affect Your Diabetes Car A comorbidity is a disease or condition that coexists with a primary disease but also stands on its own as a specific disease. The comorbidities may be physical or mental conditions. For example, someone can have hypertension (high blood pressure) and not have diabetes. But on the other hand, someone with diabetes very often has hypertension as well. So, hypertension is a common comorbidity of diabetes. Comorbidities are more common than not. The most common comorbidities in children and adolescents with type 2 diabetes are hypertension, dyslipidemia, and nonalcoholic fatty liver disease. Most adults with diabetes have at least one comorbid chronic disease and up to 40 percent have at least three. Up to 75 percent of adults with diabetes also have hypertension. Other common comorbidities of diabetes are hyperlipidemia, cardiovascular disease, kidney disease, nonalcoholic fatty liver disease, obstructive sleep apnea, and obesity. The risk factors for diabetes can also raise risks of certain types of cancer.

2.5.1.5 Risks of DM in Pregnancy:

M. A. Ramos-Arroyo et al, July 1992 in their study Maternal diabetes: The risk for specific birth defects. They studied the risk for specific birth defects among infants of mothers with gestational and chronic diabetes using data collected by the Spanish Collaborative Study of Congenital Malformations (ECEMC). For the years 1976 to 1985, they identified 10,087 infants with malformations and 9,994 control infants; 155 of the case infants and 89 of the controls were born to diabetic mothers. The crude odds ratio for any minor or major defect and insulin-treated diabetes was 5.5 (95% CI =1.2, 24.8), and for major malformations it was 8.7 (95% CI =1.8, 34.7). The risk for defects involving the central nervous system (CNS), skeletal system and cardiovascular system were significantly increased. Infants of non-insulin-treated diabetic mothers were 2.9 times more likely to have a major congenital birth defect (95% CI =1.2, 7.2): The crude odds ratio for any major or minor defect and mothers with gestational diabetes requiring insulin was 1.9 (95% CI = 1.1, 3.4). Similar risk was observed for major defects (OR =1.9, 95% CI =1.0, 3.7). These results suggest that infants of insulin-treated diabetic mothers have an increased risk of developing malformations of the CNS, cardiovascular system and skeletal system. They also found an increased risk for specific defect categories among infants of mothers with gestational diabetes treated with insulin.

2.5.1.6 Epidemiology of DM:

Yan ling et al, Sept 2014 in their study Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention found that T2DM has become an observably global public health problem. Analysis of recent statistical data reveals that T2DM has several new epidemiological characteristics. Firstly, diabetes keeps a steady increase in developed countries, such as United States and Japan. And it is worthy of note that T2DM has become a serious issue at an alarming rate in developing countries. It is predicted that T2DM will continue

to increase in the next twenty years, and more than 70% of the patients will appear in developing countries, with the majority of them being 45-64 years old Even today, seven out of top ten countries with the largest number of diabetes patients are low- or middle-income countries, including India, China, Russia, Brazil, Pakistan, Indonesia, and Bangladesh, among which the prevalence rates are 12.1% and 9.7% in India and China, respectively. Secondly, although advancing age is a risk factor for T2DM, rising rates of childhood obesity have resulted in T2DM becoming more common in children, teenagers and adolescents, which is a serious emerging of the epidemic and a new public health problem of significant proportions.

2.5.1.7 Etiology & Risk Factors of DM & GDM:

Yan ling Wet et al, Sept 2014 in their study Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention found that Type 2 diabetes is a serious and common chronic disease resulting from a complex inheritance-environment interaction along with other risk factors such as obesity and sedentary lifestyle. Type 2 diabetes and its complications constitute a major worldwide public health problem, affecting almost all populations in both developed and developing countries with high rates of diabetes-related morbidity and mortality.

Diabetes mellitus (DM) is characterized by chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism caused by complete or partial insufficiency of insulin secretion and/or insulin action. There are two primary forms of diabetes, insulin-dependent diabetes mellitus (type 1 diabetes mellitus, T1DM) and non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus, T2DM). T2DM is the most common form of DM, which accounts for 90% to 95% of all diabetic patients and is expected to increase to 439 million by 2030. In China, the latest statistical data show that diabetes and pre-diabetes are prevalent among people older than 20-year-old, with the percentages being 9.7% and 15.5% for T1DM and T2DM, respectively. T2DM mostly results from the interaction

among genetic, environmental and other risk factors. Furthermore, loss of first-phase of insulin release, abnormal pulsatility of basal insulin secretion, and increased glucagon secretion also accelerate the development of T2DM. Although T2DM patients are generally independent of exogenous insulin, they may need it when blood glucose levels are not well controlled with diet alone or with oral hypoglycemic drugs. In addition, people with T2DM are often accompanied by complications, such as cardiovascular diseases, diabetic neuropathy, nephropathy, and retinopathy. Diabetes and its associated complications lower the quality of people's lives and generate enormous economic and social burdens.

2.5.1.8 Mortality and Morbidity of DM:

Alex Fong, MD et al, 2013 in their study Pre-gestational versus gestational diabetes: A population based study on clinical and demographic differences found that diabetes complicates approximately 6%–7% of pregnancies in the United States, with California demonstrating a similar prevalence of 7.6% (Lawrence, Contreras, Chen, & Sacks, 2008). Approximately 85% are attributed to gestational diabetes mellitus (GDM), while the remaining are due to pre-gestational diabetes mellitus (PGDM).

GDM is currently defined by the American Diabetes Association as “any degree of glucose intolerance with onset or first recognition during pregnancy”(Diagnosis & classification of diabetes mellitus, 2012). The pathogenesis is typically attributed to insulin resistance during pregnancy due to factors such as human placental lactogen and tumor necrosis factor alpha (Metzger et al, 2008- Vambergue et al, 2002). PGDM, on the other hand, includes both type I and type 2 diabetes mellitus (DM) occurring prior to pregnancy.

Previous studies have reported on morbidities of both PGDM and GDM in pregnancy which include fetal macrosomia, neonatal hypoglycemia, perinatal mortality, polyhydramnios, and increased risk of cesarean delivery (Gestational

diabetes mellitus, 2004 Macintosh et al, 2006 Persson, Norman, & Hanson, 2009). However, few studies have looked at direct comparisons of morbidity between subjects with PGDM and GDM. Given PGDM's ability to affect the maternal–fetal dyad at an earlier gestational age, we hypothesize that there will be increased morbidity of PGDM when compared to GDM in all periods of pregnancy (pre-pregnancy, antepartum, and delivery).We also postulate that there will be certain racial predilections towards developing GDM and PGDM. We hypothesize that our results will confirm advancing maternal age to be associated with an increased risk of both conditions. Finally, we believe that incidences of both diseases have increased over time.

2.5.1.9 Management of Diabetes in Pregnancy:

Saurabh Ram Biharila et al, in their study Role of self-care in management of diabetes mellitus found that diabetes mellitus (DM) is a chronic progressive metabolic disorder characterized by hyperglycemia mainly due to absolute (Type 1 DM) or relative (Type 2 DM) deficiency of insulin hormone. World Health Organization estimates that more than 346 million people worldwide have DM. This number is likely to more than double by 2030 without any intervention. The needs of diabetic patients are not only limited to adequate glycemic control but also correspond with preventing complications; disability limitation and rehabilitation. There are seven essential self-care behaviors in people with diabetes which predict good outcomes namely healthy eating, being physically active, monitoring of blood sugar, compliant with medications, good problem-solving skills, healthy coping skills and risk-reduction behaviors. All these seven behaviors have been found to be positively correlated with good glycemic control, reduction of complications and improvement in quality of life. Individuals with diabetes have been shown to make a dramatic impact on the progression and development of their disease by participating in their own care. Despite this fact, compliance or adherence to these activities has been found to be low, especially when looking at long-term changes. Though multiple demographic, socio-economic and social

support factors can be considered as positive contributors in facilitating self-care activities in diabetic patients, role of clinicians in promoting self-care is vital and has to be emphasized. Realizing the multi-faceted nature of the problem, a systematic, multi-pronged and an integrated approach is required for promoting self-care practices among diabetic patients to avert any long-term complications.

American Diabetes Association 2017 found that Lifestyle management is a fundamental aspect of diabetes care and includes diabetes self-management education (DSME), diabetes self-management support (DSMS), nutrition therapy, physical activity, smoking cessation counseling, and psychosocial care. Patients and care providers should focus together on how to optimize lifestyle from the time of the initial comprehensive medical evaluation, throughout all subsequent evaluations and follow-up, and during the assessment of complications and management of comorbid conditions in order to enhance diabetes care.

2.5.2 Hypertension:

2.5.2.1 Definition of HT During Pregnancy:

The American College of Obstetricians & Gynecologists in September 2014 defined the Pre-existing HT as the pressure of the blood against the blood vessel walls each time the heart contracts (squeezes) to pump the blood through body. High blood pressure also is called hypertension. Hypertension can lead to health problems. During pregnancy, severe or uncontrolled hypertension can cause complications for mother and fetus. Chronic hypertension is high blood pressure that was present before became pregnant or that occurs in the first half (before 20 weeks) of pregnancy. If took blood pressure medication before pregnancy even if blood pressure is normal that means chronic hypertension.

The American College of Obstetricians & Gynecologists in September 2014 also defined the gestational hypertension (GHT) as a high blood pressure that first occurs in the second half (after 20 weeks) of pregnancy. Although gestational

hypertension usually goes away after childbirth, it may increase the risk of developing hypertension in the future.

Michael P Carson et al, May 2016 found that hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies. Hypertensive disorders during pregnancy are classified into 4 categories, as recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy: chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy). This terminology is preferred over the older but widely used term "pregnancy-induced hypertension" (PIH) because it is more precise.

In 2008, the Society of Obstetricians and Gynecologists of Canada (SOGC) released revised guidelines that simplified the classification of hypertension in pregnancy into 2 categories, preexisting or gestational, with the option to add "with preeclampsia" to either category if additional maternal or fetal symptoms, signs, or test results support this.

2.5.2.2 Incidence:

The Pre-eclampsia Foundation in May 2013 found that incidence rates for preeclampsia which is worst complication of HT during pregnancy, alone - in the United States, Canada and Western Europe, range from 2-5%. In the developing world, severe forms of preeclampsia and eclampsia are more common, ranging from a low of 4% of all deliveries to as high as 18% in parts of Africa. The variation in incidence rates is driven by the diversity of definitions and other criteria (including procedures, tests and their methodologies). In Latin America, preeclampsia is the first cause of maternal death.

Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related

hypertensive disorders. And, the number of babies who die from these disorders is thought to be on the order of 500,000 per annum.

In developing countries, a woman is seven times as likely to develop preeclampsia than a woman in a developed country. From 10-25% of these cases will result in maternal death.

2.5.2.3Prevalence of HT during pregnancy:

Mitsumasa Umesawa et al, 2017 in their study Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis, found that hypertensive disorders in pregnancy (HDP) represent some of the most important problems faced by public health because HDP is a major cause of maternal and prenatal morbidity and mortality. Several epidemiological studies have been performed to determine the prevalence and risk factors of HDP as well as its subtypes. The prevalence of HDP, gestational hypertension and preeclampsia are 5.2–8.2%, 1.8–4.4% and 0.2–9.2%, respectively. Body mass index, anemia and lower education appear to be modifiable risk factors for HDP. Maternal age, primiparous, multiple pregnancy, HDP in previous pregnancy, gestational diabetes mellitus, preexisting hypertension, preexisting type 2 diabetes mellitus, preexisting urinary tract infection and a family history of hypertension, type 2 diabetes mellitus and preeclampsia appear to be nonmodifiable risk factors. Genetic variants including a single-nucleotide polymorphism in the angiotensinogen gene have also been reported to be nonmodifiable risk factors. Epidemiological studies have recently examined the associations between a history of HDP and its subtypes and future risks of other diseases. These studies have reported associations between a history of HDP and a risk of coronary heart disease, heart failure, dysrhythmia, stroke, hypertension, diabetes mellitus, end-stage renal dysfunction and cardiomyopathy. HDP is not associated with the future incidence of total cancer. In conclusion, HDP is not a rare complication of pregnancy and the

influence of HDP remains for an extended duration. Physicians should consider the effects of HDP when treating chronic diseases in women.

2.5.2.4 Etiology & Risk factors for high blood pressure during pregnancy:

Cheryl Bird et al, May 2017 found that preeclampsia is a pregnancy disorder that involves high blood pressure along with other symptoms, such as protein in the urine. Other names for preeclampsia include toxemia, pregnancy-induced hypertension (PIH), and gestosis. Preeclampsia is one of four hypertensive disorders of pregnancy and can be very serious for pregnant women and their babies. If you have high blood pressure during your pregnancy, your doctor will want to find out if preeclampsia is the cause.

Doctors aren't sure what causes preeclampsia. The formation and implantation of the placenta seem to play a role, but this isn't always the case. There are many women with placentas that form normally who develop the disorder, and there are many women with poorly formed placentas who go on to have healthy pregnancies.

Although doctors don't know what causes preeclampsia, they do know that certain women are at greater risk than others. Risk factors include: First pregnancy, teen pregnancy, obesity, chronic hypertension, diabetes, twin/multiple pregnancy, previous history of preeclampsia, advanced maternal age, and donor egg pregnancies. Because these risk factors are so broad, doctors test every pregnant woman for signs of preeclampsia by measuring blood pressure and checking the urine for protein, usually at every prenatal appointment.

Unhealthy lifestyle choices may lead to high blood pressure during pregnancy. Being overweight or obese, or not staying active, are major risk factors for high blood pressure. Women experiencing their first pregnancy are more likely to have high blood pressure. Fortunately, there’s a lower chance of this condition in subsequent pregnancies with the same partner. Women carrying multiples are more likely to develop hypertension, as their body is under additional stress. Maternal age is also a factor, with pregnant women over the age of 40 being more at risk. According to the American Society for Reproductive Medicine, using

assistive technologies (such as IVF) during the conception process can increase chances of high blood pressure in a pregnant woman. Women who had high blood pressure before pregnancy are at higher risk for related complications during pregnancy than those with normal blood pressure. (Health line Media 2005-2018)

2.5.2.5 Mortality of HT During Pregnancy:

Preeclampsia Foundation in May 2013 founded that approximately 800 women die from pregnancy or childbirth-related complications around the world every day. Ninety-nine percent occur in developing countries. The higher number of maternal deaths in some areas of the world reflects inequities in access to health services and the gap between rich and poor.

The complications that account for 80% of all maternal deaths are: severe bleeding (mostly bleeding after childbirth), infections (usually after childbirth), high blood pressure during pregnancy (preeclampsia and eclampsia), and unsafe abortion. The remaining 20% are associated with diseases such as malaria and AIDS during pregnancy.

Maternal health and newborn health are closely linked. More than 3 million newborn babies die every year, and an additional 2.6 million babies are stillborn. The risk of maternal mortality is highest for adolescent girls under 15 years old. Women in developing countries have on average many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher. The probability that a 15-year-old woman will eventually die from complications of pregnancy is 1 in 150 in developing countries versus 1 in 3800 in developed countries.

2.5.2.6 Management of HT During Pregnancy:

The American College of Obstetricians & Gynecologists in September 2014 found that blood pressure will be monitored closely throughout pregnancy. BP may need

to monitor at home. Ultrasound exams may be done throughout pregnancy to track the growth of fetus. If growth problems are suspected, additional tests may be done that monitor the fetus health. This testing usually begins in the third trimester of pregnancy.

If hypertension is mild, blood pressure may stay that way or even return to normal during pregnancy, and medication may be stopped or dosage decreased. If hypertension is sever or have health problems related to hypertension, may need to start or continue taking blood pressure medication during pregnancy.

2.5.2.7Preventing of HT and Complications in Women at Increased Risk: Laura A. Magee, MD, Vancouver BC et al, in their study Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy: Executive Summary women at increased risk of preeclampsia are most commonly identified by a personal or family history of an HDP, chronic medical disease, and/or abnormal uterine artery Doppler before 24 weeks' gestation. Combining clinical, biochemical, and/or ultrasonographic risk markers may better identify women at increased preeclampsia risk however, no intervention trial has used such an approach to evaluate preventative therapy.

Recommendations are:

- Low-dose acetylsalicylic acid and calcium supplementation (of at least 1 g/d) for women with low calcium intake are recommended for preventions of preeclampsia in women at high risk.
- Acetylsalicylic acid should be: taken in a low dose (75–162mg/d), (III-B) administered at bedtime, (I-B) initiated after diagnosis of pregnancy but before 16 weeks' gestation, (I-B) and considered for continuation until delivery.
- Prophylactic doses of low-molecular-weight heparin may be discussed in women with previous placental complications (including preeclampsia) to prevent the recurrence of severe or early-onset preeclampsia, preterm delivery, and/or infants complications.

Chapter Three

Materials and Methods

3.1 Materials:

3.1.1 Patients:

The study was an experimental clinical study carried out in Khartoum state in Khartoum city the capital of Sudan, in Omdurman Medical Corp Hospital. The study started in October 2015, finished in February 2019, in which a group of (143) diabetic, and hypertensive pregnant women were under go US examination for antenatal care. Another group of (20) healthy volunteers were selected as a control group, and a gray scale procedure was done for them in order to establish some preliminary data of the population.

3.1.2 Machine:

We use 2D Mindary ultrasound machine using gray scale type.

3.2 Methods:

3.2.1 Technique:

The examination began with subject supine. First a fast scan is done to survey all uterus and its content. Then a scan with details is done to evaluate and asses the heartbeat, gestational age, placenta site, amniotic fluid volume, presentation and measure the fetal weight and finally if there are any fetal anomalies is detected.

The first organ assessed is the heart, normal heart beat is about (120-180) per minutes (if less than 120 per minute known as Brady cardia, if more than 180 per minute known as Techy cardia). Second gestational age is determine using different measurements depend on the trimester : in 1^{st} trimester we use gestational sac age (GSA) in which we measure the length of (GS), and this is in early 1^{st} trimester, at late in 1^{st} trimester we use Crown Rump Lump (CRL) in which we measure from head to rump (the lower extremities must not be included in the measurement). In 2ed trimester we use Bi-Parietal-Diameter (BPD). In the 3ed trimester we use in measurement Femoral Length (FL), Abdominal circumference

(AC), and Head Circumference (HC). Placenta site is named anterior when attached to the anterior wall, posterior if attached to the posterior wall, fundal if attached to the fundus of the uterus. If placenta near the cervix it named placenta previa and this when it is about less than 2cm from the cervix edge but we cannot say previa except after 28 weeks, but when near cervix but more than 2cm it called as low laying placenta. Amniotic fluid is evaluate by measuring a pocket free from fetus part, normal range between (5-8cm) ,(4cm) is consider as border line of oligohydramnios, (less than 4cm is known as oligohydramnios), (9cm) is consider as border line, more than (9cm) is known as polyhydramnios. Finally fetus is assessed for anomalies.

In our study we did a complete scan for the pregnant women but we just interested in placenta site, amniotic fluid volume, intrauterine fetal death, and fetal anomalies.

3.2.2 Image presentation

Ultrasound images were presented and diagnosis is confirmed by the radiologist who exist at time of scan, me and my colleges.

3.2.3 Statistic studies

SPSS was used to analyze the data to find the significant difference between variables of pregnant diabetic, hypertensive pregnant women.

Variables used for data collection are maternal age, history of DM/HT gestational age, placenta site, amniotic fluid volume, previous abortion or IUFD due to DM/HT or both, and fetal anomalies if detected.

3.2.4 Ethical consideration

The researcher got an ethical approval from Omdurman Medical Corp - Sudan and other hospitals in Khartoum city, in which the study was carried out to collect the data from the patient for the research and verbal consent from the patient and their relatives.

Chapter Four

Results

The following chapter will highlight the results of scanning of 143 diabetic and hypertensive pregnant women in Khartoum City, Khartoum State in Sudan in view of bars and tables, correlation, and ultrasound scanning results.

Table (4.1) The frequency distribution of age groups:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	–25	37	25.9	25.9	25.9
	26 – 40	97	67.8	67.8	93.7
	above 40	9	6.3	6.3	100.0
	Total	143	100.0	100.0	

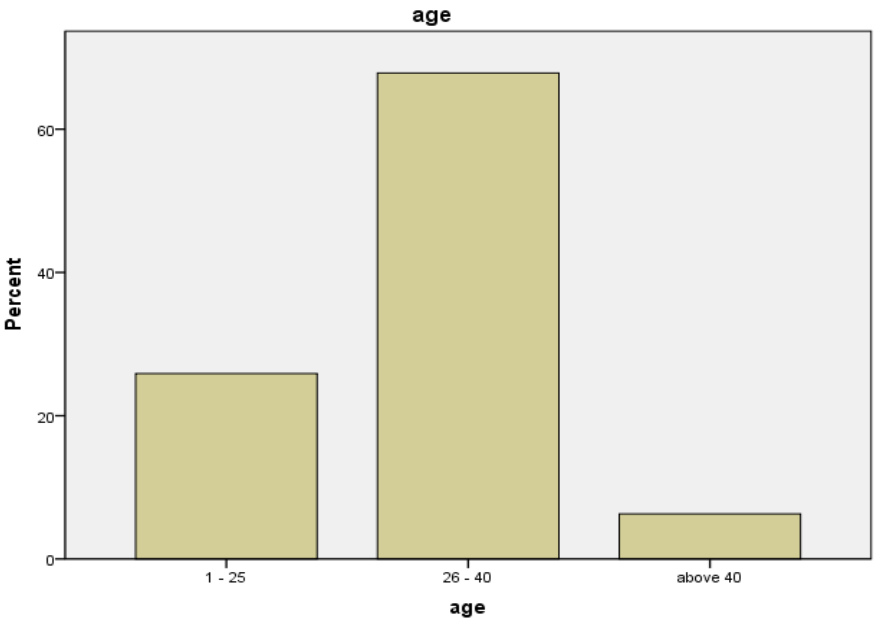


Figure 4.1 A bar plot shows the percentage of age group distribution

Table (4.2) The incidence of DM/HT:

DM/HT

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	GDM	41	28.7	28.7	28.7
	HT	71	49.7	49.7	78.3
	DM,HT	1	.7	.7	79.0
	PDM	30	21.0	21.0	100.0
	Total	143	100.0	100.0	

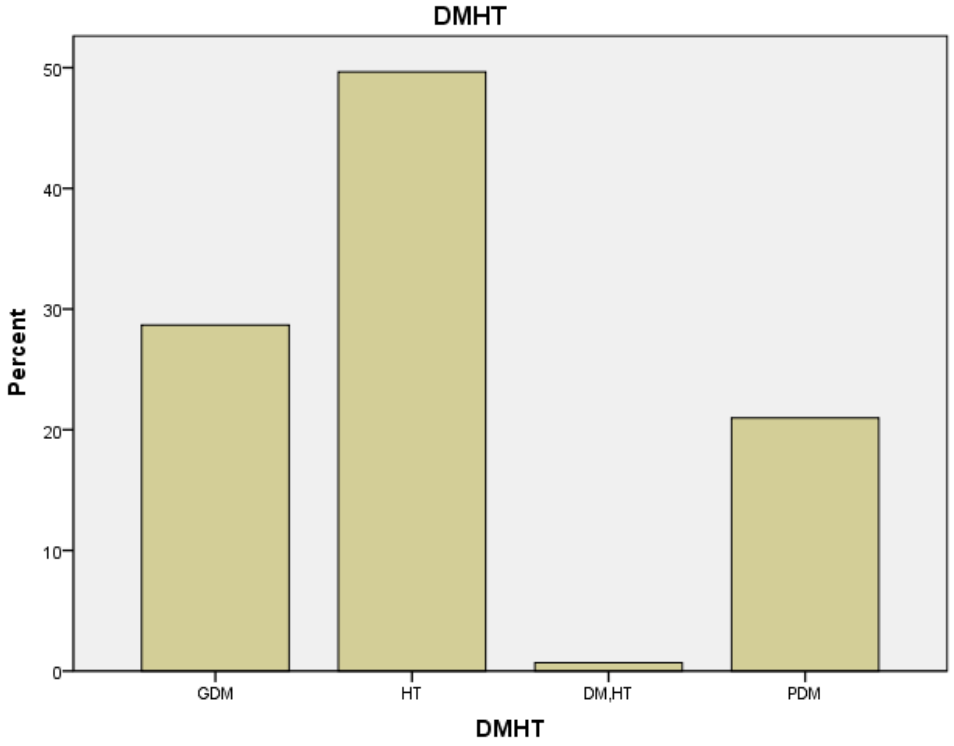


Figure (4.2) The incidence of DM/HT

Table (4.3) The patient with FH of DM/HT:

FH

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	95	66.4	66.4	66.4
	NO	48	33.6	33.6	100.0
	Total	143	100.0	100.0	

Figure (4.3) The patient with family history of DM/HT

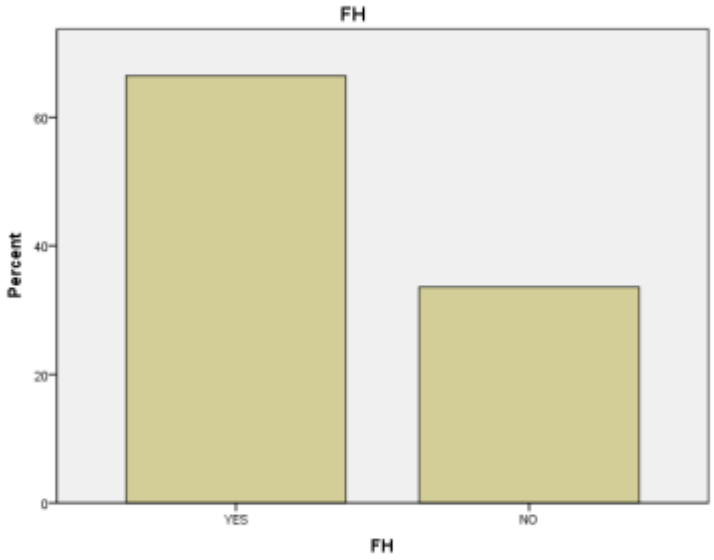


Table (4.4) The percentage of volume of amniotic fluid in the sample:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	average	125	87.4	87.4	87.4
	Oligohydr amnios	9	6.3	6.3	93.7
	Poly	9	6.3	6.3	100.0
	Total	143	100.0	100.0	

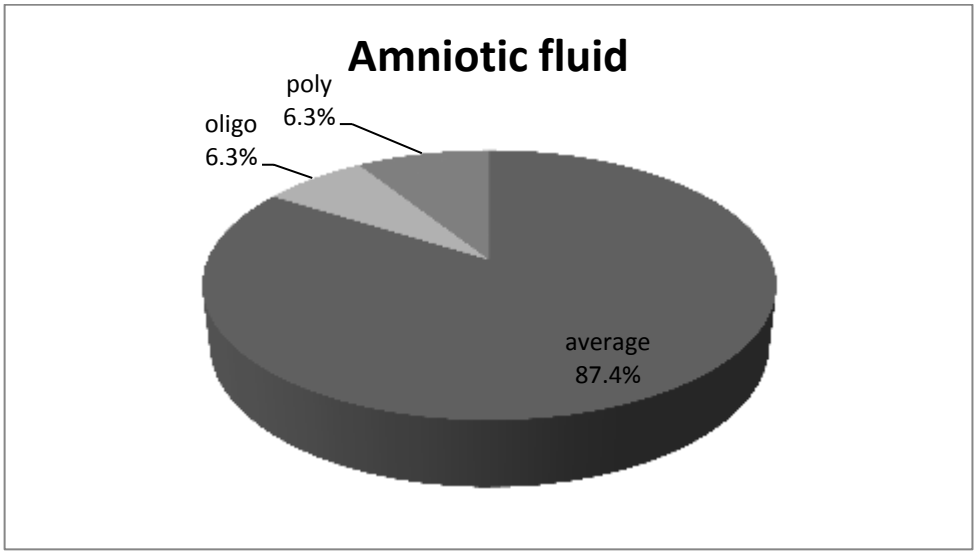


Figure (4.4) Par graph shows the percentage of volume of amniotic fluid in the sample

Table (4.5) The frequency distribution of placenta site:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	.00	7	4.9	4.9	4.9
	Normal	132	92.3	92.3	97.2
	low lying	3	2.1	2.1	99.3
	Abruption	1	.7	.7	100.0
	Total	143	100.0	100.0	

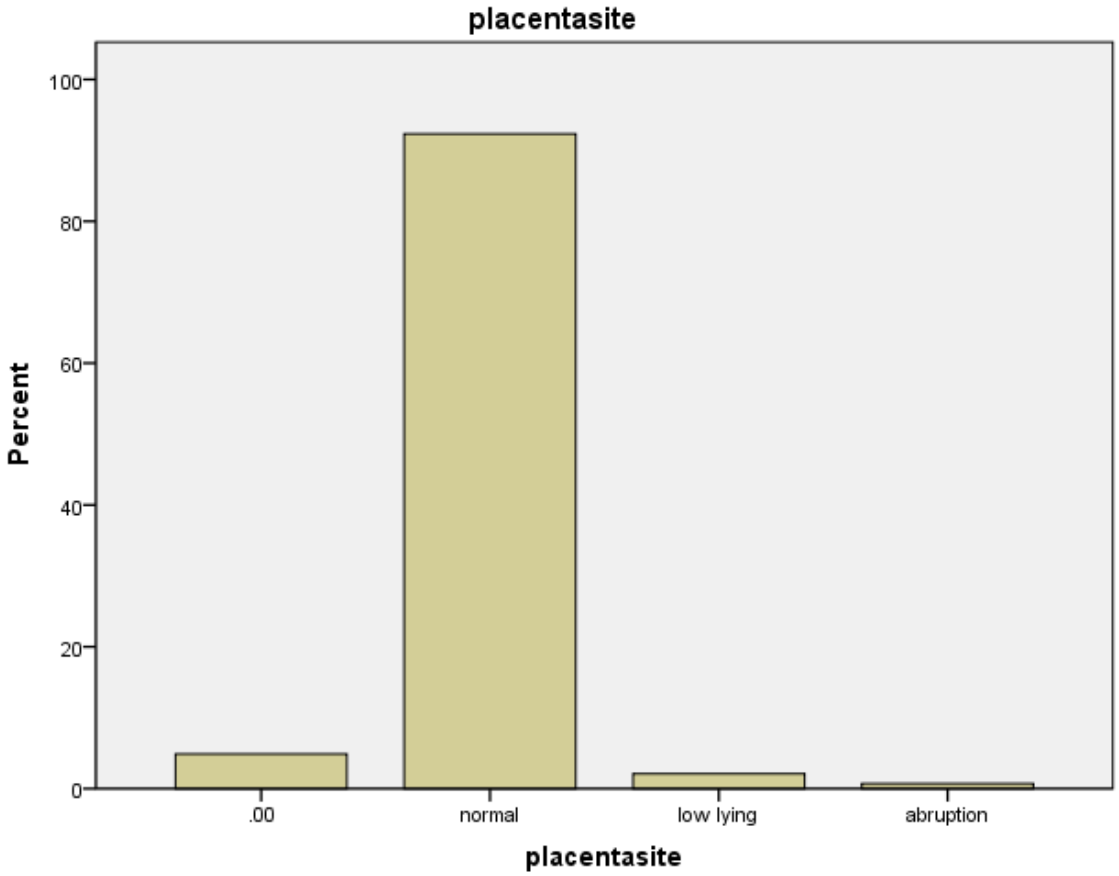


Figure (4.5) The placenta site distribution of the sample

Table (4:6) The incidence percentage of abortion:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	27	18.9	18.9	18.9
	No	116	81.1	81.1	100.0
	Total	143	100.0	100.0	

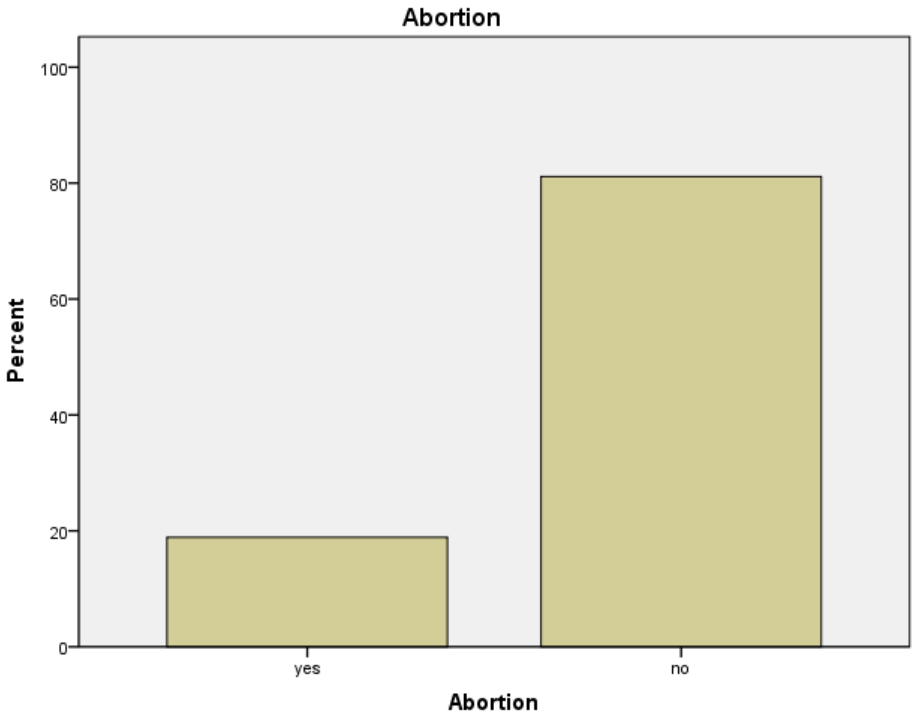


Figure (4.6) Bar graph shows the incidence of abortion between the diabetic and hypertensive pregnant women

Table(4.7) The incidence of intrauterine fetal death IUFD:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	YES	14	9.8	9.8	9.8
	NO	129	90.2	90.2	100.0
	Total	143	100.0	100.0	

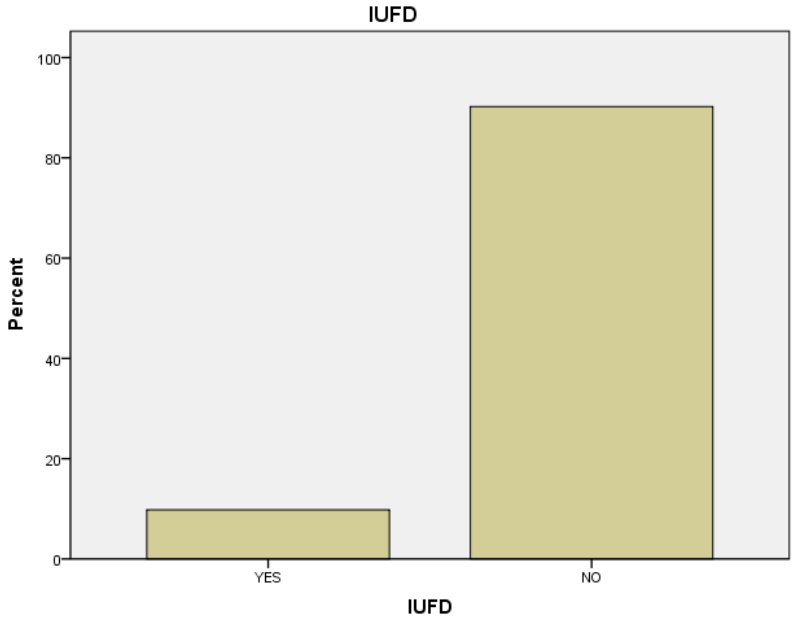


Fig (4.7) The incidence of intrauterine fetal death IUFD

Table (4.8) The incidence of fetal anomalies:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	9	6.3	6.3	6.3
	no	134	93.7	93.7	100.0
	Total	143	100.0	100.0	

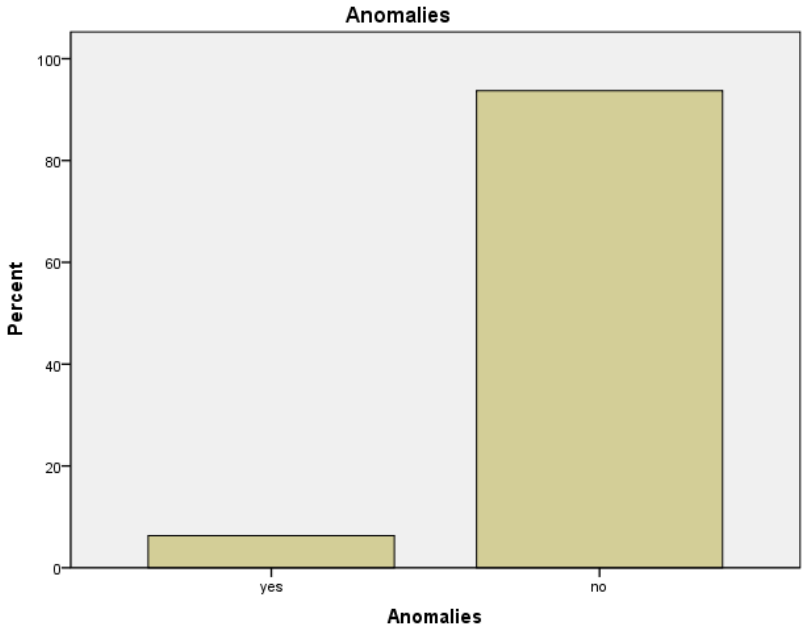


Figure (4.8) The incidence of fetal anomalies between the sample

Table(4.9) The final diagnosis of ultrasound exam for the sample:

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	88	61.5	61.5	61.5
	Abortion	24	16.8	16.8	78.3
	IUDF	7	4.9	4.9	83.2
	Polyhydramnios	5	3.5	3.5	86.7
	Oligohydramnios	3	2.1	2.1	88.8
	Hydrocephaly	1	.7	.7	89.5
	Microcephaly	3	2.1	2.1	91.6
	fetal ascites	1	.7	.7	92.3
	SP and poly	3	2.1	2.1	94.4
	more than one	8	5.6	5.6	100.0
	Total	143	100.0	100.0	

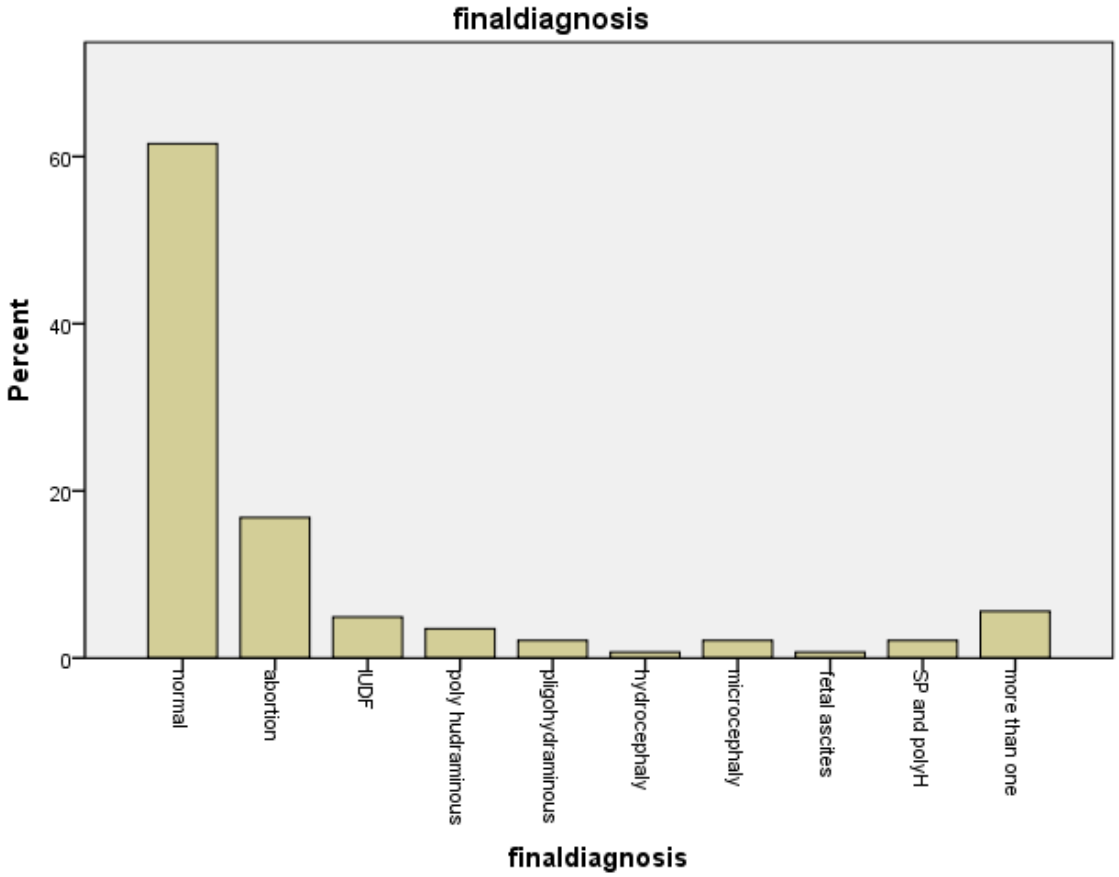


Figure (4.9) The final diagnosis of U/S scan of the sample

Table (4.10) DM/HT * age Cross tabulation:

		Age			Total
		1 - 25	26 - 40	above 40	
GDM	Count	13	28	0	41
	% within DMHT	31.7%	68.3%	.0%	100.0%
	% within age	35.1%	28.9%	.0%	28.7%
	% of Total	9.1%	19.6%	.0%	28.7%
HT	Count	17	47	7	71
	% within DMHT	23.9%	66.2%	9.9%	100.0%
	% within age	45.9%	48.5%	77.8%	49.7%
	% of Total	11.9%	32.9%	4.9%	49.7%
DM,HT	Count	0	0	1	1
	% within DMHT	.0%	.0%	100.0%	100.0%
	% within age	.0%	.0%	11.1%	.7%
	% of Total	.0%	.0%	.7%	.7%
PDM	Count	7	22	1	30
	% within DMHT	23.3%	73.3%	3.3%	100.0%
	% within age	18.9%	22.7%	11.1%	21.0%
	% of Total	4.9%	15.4%	.7%	21.0%
Total	Count	37	97	9	143
	% within DMHT	25.9%	67.8%	6.3%	100.0%
	% within age	100.0%	100.0%	100.0%	100.0%
	% of Total	25.9%	67.8%	6.3%	100.0%

Table (4.11) Chi-Square Tests DM/HT * age Cross tabulation:

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	20.201[a]	6	.003
Likelihood Ratio	13.263	6	.039
Linear-by-Linear Association	.770	1	.380
N of Valid Cases	143		

a. 6 cells (50.0%) have expected count less than 5. The minimum expected count is .06.

Table (4:12) IUFD * age Cross tabulation:

		Age			
		1 – 25	26 – 40	above 40	Total
YES	Count	3	11	0	14
	% within IUFD	21.4%	78.6%	.0%	100.0%
	% within age	8.1%	11.3%	.0%	9.8%
	% of Total	2.1%	7.7%	.0%	9.8%
NO	Count	34	86	9	129
	% within IUFD	26.4%	66.7%	7.0%	100.0%
	% within age	91.9%	88.7%	100.0%	90.2%
	% of Total	23.8%	60.1%	6.3%	90.2%
Total	Count	37	97	9	143
	% within IUFD	25.9%	67.8%	6.3%	100.0%
	% within age	100.0%	100.0%	100.0%	100.0%
	% of Total	25.9%	67.8%	6.3%	100.0%

Table (4.13) The Chi-Square Tests of age and IUFD

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.359[a]	2	.507
Likelihood Ratio	2.232	2	.328
Linear-by-Linear Association	.019	1	.892
N of Valid Cases	143		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is .88.

Table (4.14) The final diagnosis * age Cross tabulation:

Final diagnosis			Age			Total
			1 - 25	26 - 40	above 40	
Final diagnosis	Normal	Count	24	59	5	88
		% within final diagnosis	27.3%	67.0%	5.7%	100.0%
		% within age	64.9%	60.8%	55.6%	61.5%
		% of Total	16.8%	41.3%	3.5%	61.5%
	Abortion	Count	7	15	2	24
		% within final diagnosis	29.2%	62.5%	8.3%	100.0%
		% within age	18.9%	15.5%	22.2%	16.8%
		% of Total	4.9%	10.5%	1.4%	16.8%
	IUDF	Count	2	5	0	7
		% within final diagnosis	28.6%	71.4%	.0%	100.0%
		% within age	5.4%	5.2%	.0%	4.9%
		% of Total	1.4%	3.5%	.0%	4.9%
	Polyhydramnios	Count	3	2	0	5
		% within final diagnosis	60.0%	40.0%	.0%	100.0%
		% within age	8.1%	2.1%	.0%	3.5%
		% of Total	2.1%	1.4%	.0%	3.5%
	Oligohydramnios	Count	0	2	1	3
		% within final diagnosis	.0%	66.7%	33.3%	100.0%
		% within age	.0%	2.1%	11.1%	2.1%
		% of Total	.0%	1.4%	.7%	2.1%
	Hydrocephaly	Count	0	1	0	1
		% within final diagnosis	.0%	100.0%	.0%	100.0%
		% within age	.0%	1.0%	.0%	.7%
		% of Total	.0%	.7%	.0%	.7%
	Microcephaly	Count	0	3	0	3
		% within final diagnosis	.0%	100.0%	.0%	100.0%
		% within age	.0%	3.1%	.0%	2.1%
		% of Total	.0%	2.1%	.0%	2.1%
	fetal ascites	Count	0	0	1	1
		% within final diagnosis	.0%	.0%	100.0%	100.0%
		% within age	.0%	.0%	11.1%	.7%
		% of Total	.0%	.0%	.7%	.7%
	SP and poly	Count	0	3	0	3
		% within final diagnosis	.0%	100.0%	.0%	100.0%
		% within age	.0%	3.1%	.0%	2.1%
		% of Total	.0%	2.1%	.0%	2.1%
	more than one	Count	1	7	0	8
		% within final diagnosis	12.5%	87.5%	.0%	100.0%
		% within age	2.7%	7.2%	.0%	5.6%
		% of Total	.7%	4.9%	.0%	5.6%
Total		Count	37	97	9	143
		% within final diagnosis	25.9%	67.8%	6.3%	100.0%
		% within age	100.0%	100.0%	100.0%	100.0%
		% of Total	25.9%	67.8%	6.3%	100.0%

Table (4.15) Chi-Square Tests of final diagnosis and age:

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	28.080[a]	18	.001
Likelihood Ratio	20.658	18	.297
Linear-by-Linear Association	1.760	1	.185
N of Valid Cases	143		

a. 24 cells (80.0%) have expected count less than 5. The minimum expected count is .01.

Table (4.16) Final diagnosis * Amniotic fluid Cross tabulation

		Amniotic fluid			
		average	oligo	Poly	Total
Normal	Count	88	0	0	88
	% within final diagnosis	100.0%	.0%	.0%	100.0%
	% within Amniotic fluid	70.4%	.0%	.0%	61.5%
	% of Total	61.5%	.0%	.0%	61.5%
Abortion	Count	24	0	0	24
	% within final diagnosis	100.0%	.0%	.0%	100.0%
	% within Amniotic fluid	19.2%	.0%	.0%	16.8%
	% of Total	16.8%	.0%	.0%	16.8%
IUDF	Count	7	0	0	7
	% within final diagnosis	100.0%	.0%	.0%	100.0%
	% within Amniotic fluid	5.6%	.0%	.0%	4.9%
	% of Total	4.9%	.0%	.0%	4.9%
Polyhydramnios	Count	2	1	2	5
	% within final diagnosis	40.0%	20.0%	40.0%	100.0%
	% within Amniotic fluid	1.6%	11.1%	22.2%	3.5%
	% of Total	1.4%	.7%	1.4%	3.5%
Oligohydramnios	Count	0	3	0	3
	% within final diagnosis	.0%	100.0%	.0%	100.0%
	% within Amniotic fluid	.0%	33.3%	.0%	2.1%
	% of Total	.0%	2.1%	.0%	2.1%
Hydrocephaly	Count	1	0	0	1
	% within final diagnosis	100.0%	.0%	.0%	100.0%
	% within Amniotic fluid	.8%	.0%	.0%	.7%
	% of Total	.7%	.0%	.0%	.7%
Microcephaly	Count	0	3	0	3
	% within final diagnosis	.0%	100.0%	.0%	100.0%
	% within Amniotic fluid	.0%	33.3%	.0%	2.1%
	% of Total	.0%	2.1%	.0%	2.1%
fetal ascites	Count	0	1	0	1
	% within final diagnosis	.0%	100.0%	.0%	100.0%
	% within Amniotic fluid	.0%	11.1%	.0%	.7%
	% of Total	.0%	.7%	.0%	.7%
SP and poly	Count	0	0	3	3
	% within final diagnosis	.0%	.0%	100.0%	100.0%
	% within Amniotic fluid	.0%	.0%	33.3%	2.1%
	% of Total	.0%	.0%	2.1%	2.1%
more than one	Count	3	1	4	8
	% within final diagnosis	37.5%	12.5%	50.0%	100.0%
	% within Amniotic fluid	2.4%	11.1%	44.4%	5.6%
	% of Total	2.1%	.7%	2.8%	5.6%
Total	Count	125	9	9	143
	% within final diagnosis	87.4%	6.3%	6.3%	100.0%
	% within Amniotic fluid	100.0%	100.0%	100.0%	100.0%
	% of Total	87.4%	6.3%	6.3%	100.0%

Table (4. 17) Chi-Square Tests for final diagnosis and amniotic fluid:

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	205.024[a]	18	.000
Likelihood Ratio	107.057	18	.000
Linear-by-Linear Association	81.980	1	.000
N of Valid Cases	143		

a. 24 cells (80.0%) have expected count less than 5. The minimum expected count is .06.

Chapter five

Discussion, Conclusion and Recommendations

5.1 Discussion:

This study was conducted to assess pregnancy in diabetic and hypertensive women by assessing the amniotic fluid volume, placenta site as well as incidence of intrauterine fetal death, abortions and fetal anomalies in Sudan in Khartoum City using ultrasonography.
Hundred and forty three (143) pregnant diabetic and hypertensive were scanned using ultrasound to assess pregnancy status concerning the previous concerns.

The patients was distributed in three age groups as in (Table 4.1) the first group is up to 25 years old consist of 37 patients which is (25.9%) of sample, the second one from 26 years up to 40 years old, consists of 97 patient which is (67.8%) of sample, and the third group was above forty consist of 9 patients which is (6.3%) of sample. This distribution reveals that the bearing age in Sudanese women mostly around the second age group (26 years up to 40 years).

This study showed that as in tables (4.10, 4.11), increasing the age increasing the incidence of DM and HT, and consistently increased the risks associated with pregnancy in diabetic and hypertensive women as well, this agree with Jolly et al, 2000 in their study the risks associated with pregnancy in women aged 35 years or older, they found that, risk of stillbirth was significantly higher in the older women. The risks of aneuploidy and fetal congenital anomalies increase with maternal age and, despite antenatal screening, they are likely contributed to the increased rate of stillbirth.

Table (4.2) shows the incidence of gestational diabetes was 28.7% of sample (41 patient), pregestational diabetes 21% (30 patients), patient with hypertension 49,7% (71 patients), and the last patient has DM and HT was one, and the percentage was 0.7%.

In this study 66.4% of sample has family history of diabetes mellitus or hypertension (95 patient), while the rest were free 33.6% as in (Table 4.3).

Table (4.4) showed that 87.4% of the sample have normal amniotic fluid volume (125 patient), while 6.3% with polyhydramnios (9 patients), and 6.3% with oligohydramnios (9 patients). Alessia et al, 2009 in their study which concern Hypertensive Disorders of Pregnancy mentioned that, in hypertensive pregnant women usually oligohydramnios occurs; because the amniotic fluid is essentially fetal urine; with poor perfusion through the placenta, the fetus has diminished urine output. Also intrauterine demise and placental abruption are not uncommon.

IDRIS et al, 2010 in their study Influence of polyhydramnios on perinatal outcome in pregestational diabetic pregnancies found that three-hundred and fourteen pregestational diabetic pregnancies were identified during the study period, after exclusion of 10 patients with oligohydramnios of these pregestational diabetic pregnancies, 59 (18.8%) were complicated by polyhydramnios.

Table (4.5) showed that 2.1% of the sample has low laying placenta (3 patients), 0.7% has abruption placentae (one patient), and 92.3% have normal placenta site (132 patients). Alessia et al, 2009 in their study Hypertensive Disorders of Pregnancy mentioned that, the intrauterine fetal demise and placental abruption are not uncommon, in the hypertensive pregnant women. MARIJANE KROHN et al, in their study Correlates of placenta abruption, found that increased risks of placental abruption were associated with pre- eclampsia, diabetes, and unmarried status. Neither parity nor maternal age was associated with an increased risk. Infants born after abruption were significantly smaller- for- gestation than control infants, more likely to be male, and had malformations more frequently than control infants.

Table (4.7) shows that, 12% of sample have previous intrauterine fetal death, 88% of patient haven't undergoing intrauterine fetal death. This mean that DM even pregestational or gestational, or hypertension can cause intrauterine fetal death as in the study of Günter HH et al, Intrauterine fetal death in pregnancies of women

with preconceptional and gestational diabetes mellitus and of women without glucose tolerance disorders. Results of the perinatal registry of Lower Saxony, Germany (Dec 2006) The prevalence of intrauterine fetal death as well as the relevant risk factors in pregnancies of women with preconceptional and gestational diabetes mellitus.

Nandini Raghuramanet et al, 2014 in their study Hypertension-related intrauterine fetal demise in rural Haiti found that substantial portion of intrauterine fetal demise (IUFD) in low resource settings is attributed to maternal complications, including hypertension in pregnancy. The aim of the study is to describe the prevalence of IUFD in pregnant women with hypertension in a rural Haitian hospital and compare characteristics of women with hypertension who had an IUFD to those who had a live birth. Recognizing risk factors for IUFD can optimize management plans in low resource settings.

Table (4.8, 4.9), and fig (4.8, 4.9) showed that 6.3% of patient have fetus with anomalies. The anomalies are 2.1% microcephaly, 0.7% anencephaly, 0.7% fetal ascites, 2.1% spina bifida, 0.7% hydrocephalus, 0.7% undescended testes. These results agree with Victoria M. Allen, MD, MSc, FRCSC, Halifax NS et al, in their study Teratogenicity Associated With Pre-Existing and Gestational Diabetes (November 2007), which mentioned that the majority of pregnancies complicated by pre-existing and gestational diabetes are not associated with congenital abnormalities and result in the birth of healthy newborns. However, the evidence consistently confirms that pregnancies complicated by diabetes are associated with an increased risk of congenital malformations that varies with the degree of pre-conception glycemic control and other mitigating factors such as folic acid supplementation. S. Bellizzi et al, July 2016 in their study Are hypertensive disorders in pregnancy associated with congenital malformations in offspring? Evidence from the WHO Multi country cross sectional survey on maternal and newborn found that chronic hypertension in the maternal period exposes newborns to a significant risk of developing renal, limb and lip/cleft/palate congenital malformations, and the risk is further exacerbate by superimposing eclampsia.

Tables (4.12, 4.13) show that there is no significant relation between age and IUFD. And this dis agree with the study of Ling Huang et al, 2008 in their study Maternal age and risk of stillbirth: a systematic review they identified 913 unique citations, of which 31 retrospective cohort and 6 case–control studies met their inclusion criteria. In 24 (77%) of the 31 cohort studies and all 6 of the case–control studies, we found that greater maternal age was significantly associated with an

increased risk of stillbirth; relative risks varied from 1.20 to 4.53 for older versus younger women. In the 14 studies that presented adjusted relative risk, we found no extensive change in the direction or magnitude of the relative risk after adjustment. We did not calculate a pooled relative risk because of the extreme methodological heterogeneity among the individual studies. The dis agree with other studies with no justifications, but may be due to the sample.

Tables (4.10, 4.11) show that there is strong relationship between the age and incidence of DM/HT that mean when age is increased the percentage of incidence of DM/HT is increased. Ketut Suastika et al, in their study Age is an Important Risk Factor for Type 2 Diabetes Mellitus and Cardiovascular Disease(December 2012) mentioned that Metabolic disorders including type 2 diabetes mellitus (T2DM) and cardiovascular diseases are closely related with the aging process. Central obesity and insulin resistance as the initial preconditions and its consequences related to metabolic diseases and cardiovascular diseases are frequently found among the elderly**.** Thomas.W.Buford 2016, in his study Hypertension and aging mentioned that hypertension is a highly prevalent condition with numerous health risks, and the incidence of hypertension is greatest among older adults.

Tables(4.10, 4.11, 4.14, 4.15, 4.16, 4.17) show that there is significant relationship between the age and incidence of DM/HT, incidence of anomalies, abnormalities in amitotic fluid volume even polyhydramnios which is increase in amniotic fluid volume, or decrease in volume which known as oligohydramnios.

5.2 Conclusion:

This study dictated that the diabetes mellitus and hypertension are the most common and hence worse disorders occur during pregnancy, leading to many complications for mother, fetus or both.

Mother complications; like women with induced diabetes mellitus or hypertension during pregnancy may undergo later DM or HT, and with increased rate of mortality and morbidity due to undergo placenta abruption, placenta previa, pre-eclampsia, eclampsia, HELP syndrome, elevated hepatic enzyme, and hemolytic problems.

Complications to Fetus might be developed like anomalies and congenital malformations, also may be loosed due to miscarriage in early pregnancy or through intrauterine fetal death in late pregnancy.

Majority of women who have DM/HT undergo normal pregnancy and outcomes, but some of them might encounter complications with intrauterine fetal death, abortions, oligohydramnios or polyhydramnios, placenta abruption, placenta previa, fetal congenital malformations and anomalies, and stillbirth.

Age is a risk factor for incidence of DM/HT during pregnancy, and is also a risk factor of abortions, IUFD, and fetal anomalies.

In conclusion there is no significant relation between having maternal family history of DM/HT and incidence of complications of DM/HT during pregnancy, but family history increased the incidence rate of DM/HT, even preconceptional, or during pregnancy as induced HT, or GDM which consistently may lead to complications during pregnancy

5.3 Recommendations:

- Primary health care should be available for every woman anywhere, anytime for good pregnancy outcome, and this will reduce the cost of adverse outcome of pregnancy with DM/HT or even other problems which leading to pregnancy complications, such as mother mortality and morbidity, fetus anomalies, abortion, intrauterine fetal death, placenta abnormalities, amniotic fluid volume abnormalities, and stillbirth. And this is a simple human rights of women, neonates, and children to have the primary health care. And this will be approached through existence of many primary health care centers, and antenatal care centers, that which are excellent equipped.
- Community education and awareness about diabetes, and hypertension especially between women in bearing age, about the complications of DM/HT for mothers and fetus.
- Pregnancy should be planned in women with preexisting diabetes, which includes a strict metabolic control with near or near-normal glucose levels, reached through lifestyle modifications, a healthy diet, and an exercise planning program to prevent anomalies, malformations and miscarriages, and later IUFD, placenta abnormalities and amniotic fluid volume abnormality.
- Also pregestational hypertensive women should control the hypertension before being pregnant to avoid any complications of hypertension in pregnancy, through medications, lifestyle modifications, healthy diet, and an exercise.
- Ultrasonography is an easy, noninvasive, cheaper modality for assessing pregnancy, so should be available in all primary health care centers, and antenatal care centers.
- Ultrasound should be done at least three time during pregnancy, once in every trimester to see how pregnancy is going on specially with high risk pregnant women such as diabetics, and hypertensive one.

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Appendix

A

Data sheet

1.Age: 1. ---25( ) 2. 26—40 ( ) 3. 41— ( ).

2.Gravida No( ).

3. A. Diabetes Type: 1. gestional D ( ). 2. Pre gestational DM( ).

B. Hypertension: 1. Yes ( ) 2. No ( ).

C- Both ( )

4.Family history 1.Yes ( ). 2. No( ).

5. GA: …28…….week.

7. Amniotic fluid : 1. average ( ). 2.oligo ( ). 3.poly ( ).

9. If placenta is previa : 1.grade 1 ( ). 2. grade 2 ( ). 3. grade( ).

10. Previous abortion: 1. Yes ( ). 2.No ( ). If yes number ( )

11.Presence of anomalies: 1. Yes ( ). 2. No ( ). If yes where is it:

.Neurological*: Anencephaly( ) Hydrocephaly ( ) Microcephaly( ) Encephalomeningocele( )*

.Spine*: Cystic hygroma ( ) Spina bifida( )*

.Fetal GIT*: Duodenal atresia( ) Jejunal- ilial atresia( ) colonic ateresia( )*

.Urinary Tract*: Renal agenesis( ) Hypo plastic kidney( ) Renal obstruction( )*

.Skeleton*: ( )*

12. Previous IUFD: 1. Yes( ). 2. o ( ).

Comment if any other anomalies:

……

Paper 1

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Sonographic Assessment of Pregnancy in Patients with Hypertension & Diabetes

Safa Anis Hassan1, M. E. M. Garelnabi2, Muna.A. Ali3, Rania Mohammed Ahmed4
1,2,3College of Medical Radiological Science, Sudan University of Science and Technology, Khartoum, Sudan
4College of Applied Medical Science, Radiological Science Department, Taif University, Taif, Saudi Arabia

Abstract: Aim of study: This study was conducted to correlate between maternal age and incidence of fetal anomalies, as well as incidence of intrauterine fetal death, in diabetic (DM) and hypertensive (HT) pregnant women in Sudan in Khartoum City using ultrasonography. Method: Hundred pregnant women 50 diabetic, and 50 hypertensives were scanned by ultrasound to evaluate pregnancy status concerning the previous concerns. Ultrasound was used to scan pregnant diabetic or hypertensive women in the second and third trimester to see intrauterine fetal death, and fetal anomalies and malformations. The scan was done using tow dimensional Mindary machine, during the period from 2015 to 2018. Results: The study sample consists of 100 pregnant diabetic, and hypertensive pregnant females aged between 20 and 43 years old. 12 of 100 (12%) have a previous intrauterine fetal death, 88% of patient haven't undergoing intrauterine fetal death. 9 0f 100 (9%) of patient have fetus with anomalies. The anomalies were 1% microcephaly, 1% anencephaly, 1%fetal ascites, 3% spina bifida, 2% hydrocephalus, 1% undescended testes. Conclusion: Majority of women who have DM/HT undergo normal pregnancy and outcomes, but some of them might encounter complications with intrauterine fetal death, fetal congenital malformations and anomalies, and stillbirth. The incid

Key words: Ultrasonography, Diabetes mellitus, Hypertension, IUFD, Anomalies

1. Introduction:

Blood pressure is the force exerted by the blood against the walls of blood vessels, and the magnitude of this force depends on the cardiac output and the resistance of the blood vessels. Hypertension (HT), also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. [1]

High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease.

Hypertension in pregnancy should be defined as a diastolic BP of ≥ 90 mmHg or systolic BP ≥ 140 mmHg, based on the average of at least 2 measurements, taken using the same arm. Mean arterial pressure (MAP) is no longer used as a criterion in the definition of hypertension as it is difficult to calculate. Pre-existing hypertension mean pre-dates pregnancy or appears before 20 weeks, and gestational hypertension appears at or after 20 wks. [1]

Severe hypertension should be defined as a systolic BP of ≥ 160 mmHg or a diastolic BP of ≥ 110 mmHg. A repeat measurement should be taken for confirmation in 15 minutes. [2] Mean arterial pressure (MAP) is no longer used as a criterion in the definition of hypertension as it is difficult to calculate. [2]

Preeclampsia in women with pre-existing hypertension is defined as resistant hypertension, new or worsening proteinuria, or one or more adverse conditions noted below. Resistant hypertension is elevation in blood p

that requires three antihypertensive medications to control it. In women with gestational hypertension, preeclampsia is defined as new-onset proteinuria or one or more adverse conditions. Edema and weight gain have been excluded from the definition of preeclampsia. Hypertension can cause several complications during pregnancy for mother, or even to the fetus. [1] Pressure after 20 weeks gestation.

1.1 Mother Complication

Vascular and Pulmonary complications, Hepatic complication: elevated AST, ALT, LDH, Severe nausea, Jaundice. Hematologic complications: platelets <100,000, Disseminated intravascular coagulopathy (DIC). CNS complications: persistent new or unusual headache, visual disturbances, hyper reflexia, seizures, stroke, and HELLP syndrome.

1.2 Fetal complications include

- Intrauterine growth restriction (IUGR).
- Atypical / abnormal fetal heart rate.
- Intrauterine fetal death.
- Placental abruption.
- Oligo-hydramnios
- Prematurity. [3]

1.3 Diabetes Mellitus

Is the most common medical complication of pregnancy and it carries a significant risk to the fetus and the mother. [4]

Congenital malformations and perinatal morbidity remain common compared with the offspring of non-diabetic pregnancies. Diabetic mothers are at risk of progression of micro vascular diabetic complications as well as early pregnancy loss, pre-eclampsia, poly-hydramnios and premature labour. Glycemic control before and during pregnancy is critical and the benefit may result in a viable, healthy off spring. Gestational diabetes mellitus (GDM) which manifests for the first-time during pregnancy is common and, on the increase, its proper management will reduce the risk of neonatal macrosomia and hypoglycemia. Post-partum evaluation of glucose tolerance and appropriate counseling in women with GDM may help decrease the high risk of subsequent type 2 diabetes in the long term. [4]

1.4 Fetal complications include:

- Congenital anomalies: cardio-vascular central nervous system, skeletal (sacral agenesis), and genito-urinary.
- Fetal growth retardation (in diabetic pregnancy complicated by nephropathy (IUGR)
- Excessive fetal growth (macrosomia).[4]

Diabetic keto-acidosis, hypo-glycaemia, visual deterioration/retinopathy, deterioration of nephropathy, vomiting (gastric neuropathy), miscarriages, pre-eclampsia, poly-hydramnios, premature delivery are considered as maternal complications in diabetic pregnancy.[4]

2. Materials & Methods

This was an experimental clinical study carried out in Khartoum city, the capital of Sudan at Medical Corp Hospital. The study conducted from May 2015 till March 2019, in which a group of (100) diabetic and hypertensive pregnant women underwent U/S examination for antennal care. Another group of (20) healthy volunteers were selected as a control group and gray scale procedure was done for them in order to establish some preliminary data of the population.

2D Mindary ultrasound machine with Doppler facilities was used to scan the patients. The examination began with subject supine. First fast scan was done to survey all uterus and its content. Then a scan with details is done to evaluate and asses the heartbeat, gestational age, placenta site, amniotic fluid volume, presentation and asses fetal weight and finally if there is any fetal anomalies is detected.

In this study a complete scan was done for the pregnant women to detect intrauterine fetal death, placenta site, amniotic fluid volume, and fetal anomalies. Variables used for data collection are mother age, history of diabetes or hypertension, gestational age, placenta site, IUFD, previous abortions due to DM or HT, amniotic fluid volume, and fetal anomalies.

Data analyzed using SPSS to find the significant difference between the variables and the results presented in tables and graphs, significant correlation between the variables was represented in

3. Results

100 diabetic and hypertensive, pregnant women in Khartoum city, the capital of Sudan were referred to ultrasound department for ultrasound scan, they were selected randomly to participate in this study; the obtained results were analyzed and presented in tables, graphs and figures. Significant correlations between the variables were obtained.

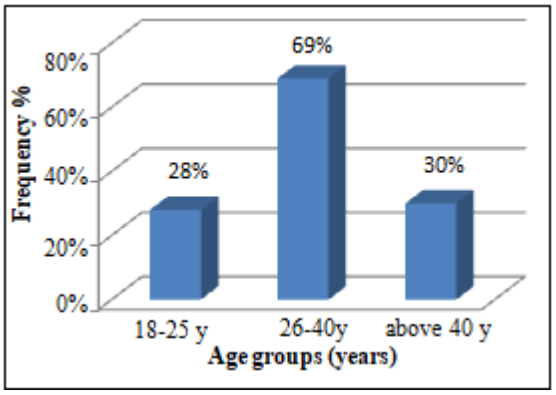

Figure 1: Shows the percentage distribution of age among study sample. (N=100)

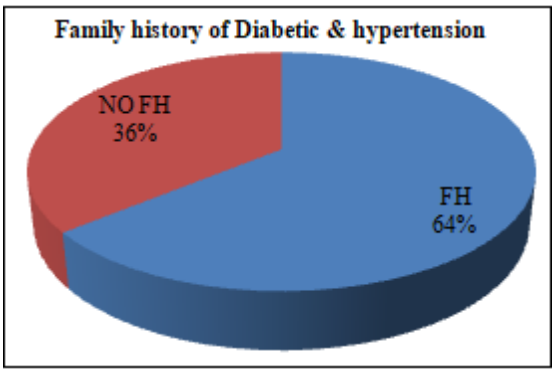

Figure 2: Shows the percentage distribution of the study sample have had family history of both HT &DM

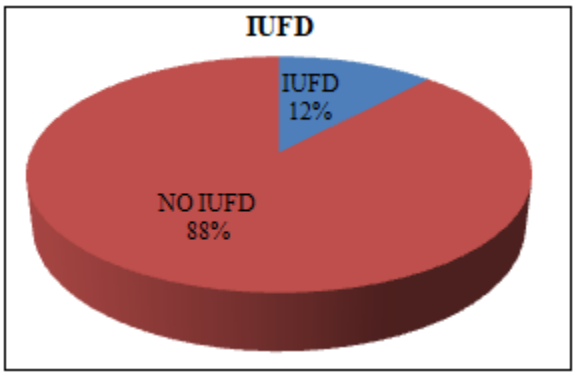

Figure 3: Shows the percentage of intrauterine fetal death (IUFD) incidence

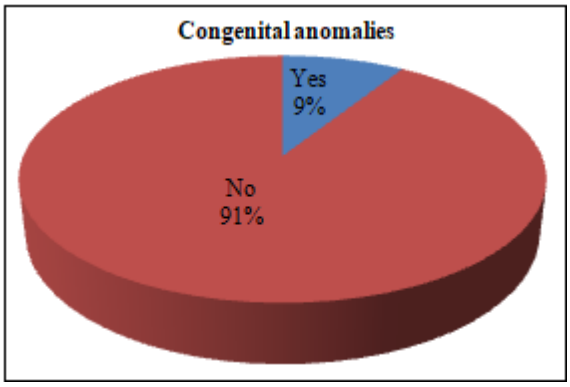

Figure 4: Show the percentage distribution of anomalies incidence

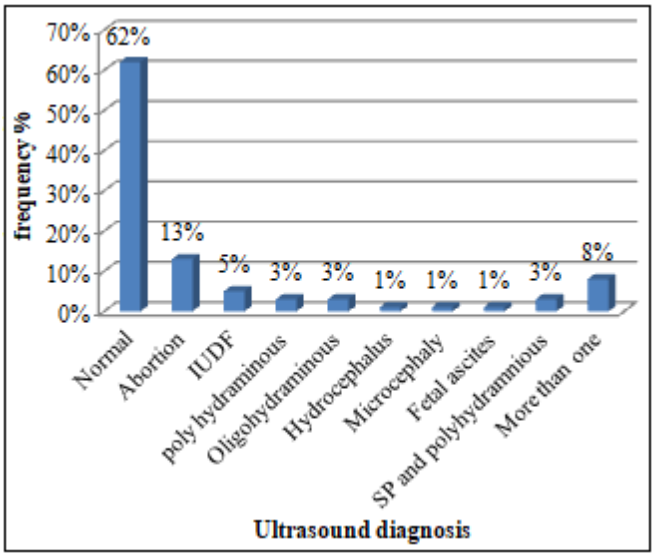

Figure 5: Shows the final ultrasound diagnosis

Table 1: The relation between study sample age groups and DM & HT incidence. (n=100) *cross tab

Age groups			DMHT				Total	Asymp. Sig. (2-sided)
			GDM	HT	DM,HT	PDM		
	18 – 25y	Count	9_a	14_a	0_a	5_a	28	0.000
		% within age	32.1%	50.0%	.0%	17.9%	100.0%	
		% within DM/HT	32.1%	28.0%	.0%	23.8%	28.0%	
		% of Total	9.0%	14.0%	.0%	5.0%	28.0%	
	26 – 40y	Count	19_a	34_a	0_a	16_a	69	
		% within age	27.5%	49.3%	.0%	23.2%	100.0%	
		% within DMHT	67.9%	68.0%	.0%	76.2%	69.0%	
		% of Total	19.0%	34.0%	.0%	16.0%	69.0%	
	Above 40y	Count	0_a	2_a	1_b	0_a	3	
		% within age	.0%	66.7%	33.3%	.0%	100.0%	
		% within DMHT	.0%	4.0%	100.0%	.0%	3.0%	
		% of Total	.0%	2.0%	1.0%	.0%	3.0%	
Total		Count	28	50	1	21	100	
		% within age	28.0%	50.0%	1.0%	21.0%	100.0%	
		% within DMHT	100.0%	100.0%	100.0%	100.0%	100.0%	
		% of Total	28.0%	50.0%	1.0%	21.0%	100.0%	
*Each subscript letter denotes a subset of DMHT categories whose column proportions do not differ significantly from each other at the .05 level.								

*There is strong correlation between the variables as (p=0.000)

Table 2: Shows Ultrasound results * Age (cross tab). (n=100)

Ultrasound diagnosis			Age			Total	Asymp. Sig. (2-sided)
			18 – 25 y	26 – 40 y	above 40 y		
	Normal	Count	22$_a$	40$_a$	0$_b$	62	0.000
		% within final diagnosis	35.5%	64.5%	.0%	100.0%	
		% within age	78.6%	58.0%	.0%	62.0%	
		% of Total	22.0%	40.0%	.0%	62.0%	
	Abortion	Count	2$_a$	10$_a$	1$_a$	13	
		% within final diagnosis	15.4%	76.9%	7.7%	100.0%	
		% within age	7.1%	14.5%	33.3%	13.0%	
		% of Total	2.0%	10.0%	1.0%	13.0%	
	IUDF	Count	2$_a$	3$_a$	0$_a$	5	
		% within final diagnosis	40.0%	60.0%	.0%	100.0%	
		% within age	7.1%	4.3%	.0%	5.0%	
		% of Total	2.0%	3.0%	.0%	5.0%	
	Poly hydramnios	Count	1$_a$	2$_a$	0$_a$	3	
		% within final diagnosis	33.3%	66.7%	.0%	100.0%	
		% within age	3.6%	2.9%	.0%	3.0%	
		% of Total	1.0%	2.0%	.0%	3.0%	
	Oligo-hydramenios	Count	0$_a$	2$_a$	1$_b$	3	
		% within final diagnosis	.0%	66.7%	33.3%	100.0%	

		% within age	.0%	2.9%	33.3%	3.0%	
		% of Total	.0%	2.0%	1.0%	3.0%	
	Hydrocephaly	Count	0a	1a	0a	1	
		% within final diagnosis	.0%	100.0%	.0%	100.0%	
		% within age	.0%	1.4%	.0%	1.0%	
		% of Total	.0%	1.0%	.0%	1.0%	
	Microcephaly	Count	0a	1a	0a	1	
		% within final diagnosis	.0%	100.0%	.0%	100.0%	
		% within age	.0%	1.4%	.0%	1.0%	
		% of Total	.0%	1.0%	.0%	1.0%	
	Fetal ascites	Count	0a	0a	1b	1	
		% within final diagnosis	.0%	.0%	100.0%	100.0%	
		% within age	.0%	.0%	33.3%	1.0%	
		% of Total	.0%	.0%	1.0%	1.0%	
	Spina bifida and poly-hydramnios	Count	0a	3a	0a	3	
		% within final diagnosis	.0%	100.0%	.0%	100.0%	
		% within age	.0%	4.3%	.0%	3.0%	
		% of Total	.0%	3.0%	.0%	3.0%	
	More than one	Count	1a	7a	0a	8	
		% within final diagnosis	12.5%	87.5%	.0%	100.0%	
		% within age	3.6%	10.1%	.0%	8.0%	
		% of Total	1.0%	7.0%	.0%	8.0%	
Total		Count	28	69	3	100	
		% within final diagnosis	28.0%	69.0%	3.0%	100.0%	
		% within age	100.0%	100.0%	100.0%	100.0%	
		% of Total	28.0%	69.0%	3.0%	100.0%	
*There is strong correlation between the variables represented as (p=0.000).							

Table 3: Shows maternal family history (FH) of DM/HT and IUFD (cross tab) (n=100)

FH	IUFD		Total	Exact Sig. (1-sided)
	Yes	No		
Yes	12	52	64	.003
No	0	36	36	
Total	12	88	100	

Table 4: Shows maternal FH of DM/HT and anomalies (cross tab). (n=100)

FH	Anomalies			Exact Sig. (1-sided)
	Yes	No	Total	
Yes	9	55	64	.01
No	0	36	36	
Total	9	91	100	

Table 5: Ultrasound diagnosis * Fetal anomalies (cross tab). (n=100)

Ultrasound diagnosis			Fetal anomalies		Total	Asymp. Sig. (2-sided)
			Yes	No		
	Normal	Count	0a	62b	62	0.000
		% within final diagnosis	.0%	100.0%	100.0%	
		% within Anomalies	.0%	68.1%	62.0%	0.000
		% of Total	.0%	62.0%	62.0%	0.000
	Abortion	Count	0a	13a	13	
		% within final diagnosis	.0%	100.0%	100.0%	
		% within Anomalies	.0%	14.3%	13.0%	
		% of Total	.0%	13.0%	13.0%	
	IUDF	Count	0a	5a	5	
		% within final diagnosis	.0%	100.0%	100.0%	
		% within Anomalies	.0%	5.5%	5.0%	
		% of Total	.0%	5.0%	5.0%	
	Poly-hydramnios	Count	0a	3a	3	
		% within final diagnosis	.0%	100.0%	100.0%	
		% within Anomalies	.0%	3.3%	3.0%	
		% of Total	.0%	3.0%	3.0%	
	Oligo-hydramnios	Count	0a	3a	3	
		% within final diagnosis	.0%	100.0%	100.0%	
		% within Anomalies	.0%	3.3%	3.0%	
		% of Total	.0%	3.0%	3.0%	
	Hydrocephaly	Count	1a	0b	1	

		% within final diagnosis	100.0%	.0%	100.0%	
		% within Anomalies	11.1%	.0%	1.0%	
		% of Total	1.0%	.0%	1.0%	
	microcephaly	Count	1[a]	0[b]	1	
		% within final diagnosis	100.0%	.0%	100.0%	
		% within Anomalies	11.1%	.0%	1.0%	
		% of Total	1.0%	.0%	1.0%	
	fetal ascites	Count	1[a]	0[b]	1	
		% within final diagnosis	100.0%	.0%	100.0%	
		% within Anomalies	11.1%	.0%	1.0%	
		% of Total	1.0%	.0%	1.0%	
	SP and poly-hydramnios	Count	3[a]	0[b]	3	
		% within final diagnosis	100.0%	.0%	100.0%	
		% within Anomalies	33.3%	.0%	3.0%	
		% of Total	3.0%	.0%	3.0%	
	more than one	Count	3[a]	5[b]	8	
		% within final diagnosis	37.5%	62.5%	100.0%	
		% within Anomalies	33.3%	5.5%	8.0%	
		% of Total	3.0%	5.0%	8.0%	
Total		Count	9	91	100	
		% within final diagnosis	9.0%	91.0%	100.0%	
		% within Anomalies	100.0%	100.0%	100.0%	
		% of Total	9.0%	91.0%	100.0%	
*Each subscript letter denotes a subset of Anomalies categories whose column proportions do not differ significantly from each other at the .05 level.						

4. Discussion

This study was conducted to evaluate pregnancy in diabetic and hypertensive women by detecting the prevalence of fetal anomalies and related risk factors (maternal age, presence of family history and amniotic fluid problems) among hypertensive and diabetic women in Sudan in Khartoum city using ultrasonography.

100 pregnant women 50 diabetic, and 50 hypertensives were scanned by gray scale and color Doppler ultrasound to assess pregnancy status concerning the previous concerns.

In this study the patients were distributed in three age groups, as in fig (1) the first age group from (18-25) years old represented (28%), (26 –40) years old represented (69%) and the third groups above forty represented (3%) of the study sample. This distribution reveals that the bearing age in Sudanese women mostly around the second age group (26 – 40) years. The study showed that, increasing age increased the incidence of DM and HT, and consistently increased the risks associated with pregnancy, in diabetic and hypertensive women as well represented as (p=0.00), as in table (1), and this agree with M. Jolly et al 2000 [5] ; who reported in their study 'the risks associated with pregnancy in women aged 35 years or older they found that, risk of stillbirth was significantly higher in the older women. The risks of fetal congenital anomalies and malformations, and aneuploidy increase with maternal age and, despite antenatal screening, they are likely contributed to the increased rate of stillbirth'.

Previous study [6], reported that 'pregnancy outcomes according to increasing maternal age reported that 29,760 singleton pregnancies delivered between 2005 and 2008 was extracted from our database. Patients were distributed into 4 groups according to age: (20– 29) years, (30–34) years, (35–39) years, and ≥40 years. Multivariable logistic regression analysis was used to evaluate the adjusted odd ratios (AORs) of adverse outcomes of pregnancy according to mother age after adjusting for parity, body mass index, medical history and use of in vitro fertilization. The result was that majority of adverse perinatal outcomes were associated with a maternal age ≥35 years as follows: low birth weight (AOR 1.2 and 1.6 for women aged 35–39 years and ≥40 years, respectively); Apgar score < 7 at 1 minute (AOR: 1.7 and 1.8); and chromosomal anomaly (AOR: 2.7 and 12.3). However, women aged ≥30 years also had greater risks for adverse maternal outcomes such as: gestational diabetes (AOR: 2.0, 3.6 and 5.1 for women aged 30–34 years, 35–39 years and ≥40 years, respectively); placenta previa (AOR: 1.6, 2.1 and 3.6); and cesarean delivery (AOR: 1.5, 2.3, and 4.1), as well as adverse fetal outcomes such as: preterm delivery (AOR: 1.2, 1.4 and 1.8) and neonatal intensive care unit transfer (AOR: 1.1, 1.2, and1.6). However, increasing maternal age is an independent and substantial risk factor for adverse perinatal and obstetric outcomes. These adverse outcomes become more common as increasing maternal age without a clear cutoff age.

Regarding family history in this study (64%) of the study sample have had positive family history for hypertension or and DM, as in fig (2).Controlled cohort studies [7,8,9] showed that the risk of pre-eclampsia is increased in women with a previous history of hypertension (relative risk 7.19, 95% confidence interval 5.85 to 8.83) , pre-existing diabetes (3.56, 2.54 to 4.99), family history (2.90, 1.70 to 4.93), raised blood pressure (diastolic ≥ 80 mm Hg) at booking (1.38, 1.01 to 1.87), raised body mass index before pregnancy (2.47, 1.66 to 3.67) or at booking (1.55, 1.28 to 1.88), or maternal age ≥ 40 (1.96, 1.34 to 2.87, for multiparous women). A family history of pre-eclampsia nearly triples the risk of pre-eclampsia (2.90, 1.70 to 4.93) (two cohort studies.

(12%) from the study sample have previous intrauterine fetal death, while (88%) of patient haven't undergoing intrauterine fetal death, as in fig (3). This mean that DM even pregestational or gestational, and or hypertension can cause intrauterine fetal death as reported in previous study by Günter HH., et al [10]; Intrauterine fetal death in pregnancies of women with preconceptional and gestational diabetes mellitus and of women without glucose tolerance disorders. Results of the perinatal registry of Lower Saxony, Germany. The prevalence of intrauterine fetal death as well as the relevant risk factors in pregnancies of women with preconceptional and gestational diabetes mellitus.

Ahmad A, et al, [11], they reported in their study 'Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2,121 and 371 pregnancies, reported that the prevalence of hypertensive disorders in pregnancy was 4.7%. In total, 17 933 fetal deaths occurred and 9.2% of these were in hypertensive pregnancies. In normotensive pregnancies, 0.8% (16 290/2 022 400) experienced fetal death. This was true for 1.9% (1170/62 261) of the pregnancies with pre-eclampsia, 1.2% (390/32 068) with gestational hypertension and 1.8% (83/4642) with chronic hypertension. There was a 44% overall reduction in fetal death rate from 1967–1986 to 1987–2006. The largest decline was in women with pre-eclampsia (80% reduction). In women with gestational hypertension and chronic hypertension, the overall reductions in fetal death rates were 49% and 57%, respectively, comparable with the 41% decline in normotensive pregnancies.

In this study and regarding congenital anomalies , there were (9%) of the study sample have had fetuses with intra-uterine congenital anomalies, as in fig (4),table (2) fetal anomalies were found to be (1%) microcephaly, (1%) anencephaly, (1%) fetal ascites, (3%) with spina bifida, (2%) hydrocephalus, (1%) undescended testes. These results agree with study by Victoria M. Allen et al, [12], they found that teratogenicity associated with pre-existing and gestational diabetes, which mentioned that the majority of pregnancies complicated by pre-existing and gestational diabetes are not associated with congenital abnormalities and result in the birth of healthy newborns. However, the evidence consistently confirms that pregnancies complicated by diabetes are associated with an increased risk of congenital malformations that varies with the degree of pre-conception glycemic control and other mitigating factors such as folic acid supplementation.

In this study and, as in table (1) shows that there is strong relationship between the age and incidence of DM/HT that mean when age is increase the percentage of incidence of DM/HT is increased represented in (p=0.000).In this study demonstrated a significant relationship between the age and incidence of anomalies, abnormalities represented in (p=0.000) , as in table (2). Ketut S et al, [13] found that; age is an important risk factor for type 2 Diabetes Mellitus and cardiovascular disease. Central obesity and insulin resistance as the initial preconditions and its consequences related to metabolic diseases and cardiovascular diseases are frequently found among the elderly. Thomas W, et al.,[14] in his study about hypertension and aging reported that; 'hypertension is a highly prevalent condition with numerous health risks, and the incidence of hypertension is greatest among older adults'.

This study reported strong co- relation between maternal family history of IUFD and presence of fetal anomalies as reported in the sonographic imaging results among positive cases of the study sample with (p=0.003,0.01&0.00) respectively, as in tables (3,4&5) and fig (5). Study by Simerpal K. Gill et all, [15] found that, there is A strong association between Maternal Age and birth defects of unknown etiology, for maternal age <20 years, associations with total anomalous pulmonary venous return mention that (a OR, 2.3; 95% CI, 1.3–4.0), and gastroschisis (a OR, 6.1; 95% CI, 4.8–8.0) were observed. For the ≥40-year age group, associations with several cardiac defects, esophageal atresia (a OR, 2.9; 95% CI, 1.7–4.9), hypospadias (a OR, 2.0; 95% CI, 1.4–3.0), and craniosynostosis (a OR, 1.6; 95% CI, 1.1–2.4) were observed. Results using maternal age as a continuous variable were consistent with those that used categorized maternal age.

Pre-eclampsia was seldom divided into early and late onset, nor were results presented for onset of pre-eclampsia or delivery in relation to gestational age. We may therefore have underestimated the

importance of risk factors for early onset pre-eclampsia, a type with considerable maternal and perinatal morbidity and mortality. [16,17]

K Cambra[18] reported that; trends in the prevalence of congenital anomalies and age at motherhood in a southern European region: a population-based study mentioned that in the Basque Country, rates of chromosomal anomalies are higher than the overall estimated prevalence in European countries, and continue to increase slightly, which may be related to the rise in maternal age. Rates of non-chromosomal anomalies are within the European frequent range of values, and the increases observed need to be checked in the following years.

5. Conclusion

This study concluded that Age is a risk factor for incidence of DM/HT during pregnancy, and is also a risk factor of abortions, IUFD, and fetal anomalies. Age is a risk factor for incidence of DM/HT during pregnancy, and is also consistently risk factor of DM, HT complications such as abortions, placenta site abnormalities, polyhydramnios, oligohydramnios, IUFD, and fetal anomalies. Diabetes mellitus and hypertension are the most common and hence worse disorders occur during pregnancy, leading to many complications for mother, fetus or both. Mother complications; like women with induced diabetes mellitus or hypertension during pregnancy may undergo later DM or HT, and with increased rate of mortality and morbidity. Complications to Fetus might be developed like anomalies and congenital malformations, also may be loosed due to miscarriage in early pregnancy or through intrauterine fetal death in late pregnancy. Majority of women who have DM/HT undergo normal pregnancy and outcomes, but some of them might encounter complications with intrauterine fetal death, abortions, oligohydramnios or polyhydramnios as complications of DM.

6. Recommendations

 Primary health care should be available for every woman anywhere, anytime for good pregnancy outcome, and this will reduce the cost of adverse outcome of pregnancy with DM/HT or even other problems which leading to complications, such as mother mortality and morbidity, fetus anomalies, abortion, intrauterine fetal death, placenta abnormalities, amniotic fluid volume abnormalities, and stillbirth. And this is simple human rights of women, neonates, and children to have the primary health care. And this will be approached through existence of many primary health care centers, and antenatal care centers, that which are excellent equipped.

 Majority of women who have DM/HT undergo normal pregnancy and outcomes, but some of them might encounter complications with intrauterine fetal death, abortions, oligohydramnios or polyhydramnios, placenta abruption, placenta previa, fetal congenital malformations and anomalies, and stillbirth. Age is a risk factor for incidence of DM/HT during pregnancy, and is also a risk factor of abortions, IUFD, and fetal anomalies.

 Implementation of community education and awareness about diabetes, and hypertension especially between women in bearing age, about the complications of DM/HT for mothers and fetus is mandatory in Sudan.

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PAPER 2

ASSESSMENT OF AMNIOTIC FLUID VOLUME IN DIABETIC AND HYPERTENSIVE WOMEN USING ULTRASOUND

Safa Anis Hassan	College of Medical Radiological Science, Sudan University of Science and Technology Khartoum. Sudan
M. E. M. Garelnabi	College of Medical Radiological Science, Sudan University of Science and Technology Khartoum. Sudan
Muna. A. Ali	College of Medical Radiological Science, Sudan University of Science and Technology Khartoum. Sudan
Nagwan Elhussein	Radiology Department, College of Applied Medical Sciences, University of Hail

Method: this prospective study was performed in a period from May 2017 to Dec 2018, one hundred pregnant women were scanned by ultrasound machine to assess the amniotic fluid volume, 50 pregnant women have diabetes mellitus and 50 have hypertensive in the second and third trimester at Medical Corp Hospital, in Khartoum city, Sudan. **Data collection:** the data was collected using data sheet which include (maternal age, history of diabetes or hypertension, gestational age, placenta site, intrauterine fetal death (IUFD), previous abortions due to diabetes or hypertension, amniotic fluid volume and fetal anomalies). **Data analysis:** data was analyzed using SPSS to find the significant difference between the variables and the results presented in tables and graphs, significant correlation between the variables was represented in value(p=0.005). **Results:** 9% of sample was with polyhydramnios, and 7% of sample has, 84% haven't undergone complications. **Conclusion:** diabetes and hypertension can cause polyhydramnios or oligohydramnios in pregnant women which may lead to worse outcomes to mother, and even fetus. Ultrasonography, Diabetes mellitus, Hypertension, Polyhydramnios, Oligohydramnios.

INTRODUCTION:

The amniotic fluid which fetus bathes is necessary for its proper growth and development. It cushions the fetus from physical trauma, permits fetal lung growth, and provides a barrier against infection. Normal amniotic fluid volume varies. The average volume increases with gestational age, peaking at 800-1000 mL, which coincides with 36-37 weeks' gestation. An abnormally high level of amniotic fluid, polyhydramnios, alerts the clinician to possible fetal anomalies. An inadequate volume of amniotic fluid, oligohydramnios, results in poor development of the lung tissue and can lead to fetal death [1]

Polyhydramnios is defined as a pathological increase of amniotic fluid volume in pregnancy and is associated with increased perinatal morbidity and mortality [2]. Also, polyhydramnios is defined as an abnormally large level of amniotic fluid during pregnancy. It is defined by an amniotic fluid index that is above the 95th centile for gestational age [3]. Polyhydramnios occurs in 1% of pregnancies, whereas oligohydramnios occurs in about 11% of pregnancies. [1]

The diagnosis is obtained by ultrasound. The prognosis of polyhydramnios depends on its cause and severity. Typical symptoms of polyhydramnios include maternal dyspnea, preterm labor, and premature rupture of membranes, abnormal fetal presentation, cord prolapse and postpartum hemorrhage. Due to its common etiology with gestational diabetes, polyhydramnios is often associated with fetal macrosomia [1]

Polyhydramnios is idiopathic in 50-60% of cases [3]. Other causes are:

Maternal diabetes, fetal malformations, multiple gestation fetal anemia, other fetal disorders (eg,

infections) or genetic abnormalities, any condition that prevents the fetus from swallowing – e.g. esophageal atresia, CNS abnormalities, muscular dystrophies, congenital diaphragmatic hernia obstructing the esophagus ,duodenal atresia – 'double bubble' sign on ultrasound scan, anaemia – alloimmune disorders, viral infections, fetal hydrops, twin-to-twin transfusion syndrome, increased lung secretions – cystic adenomatoid malformation of lung, maternal

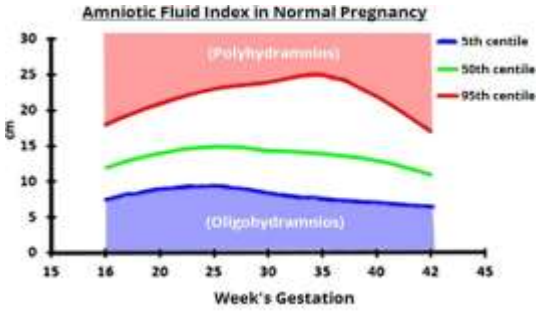

Fig (1) Amniotic fluid centiles during pregnancy. Polyhydramnios is over the 95th centile, oligohydramnios is below the 5th centile [3]

Material: This study was prospective study carried out in Medical Corp Hospital in Khartoum city, Sudan, in a period from May 2017 till December 2018.

Study sample: In which a group of (100) diabetic, and hypertensive pregnant women underwent U/S examination for antennal care. Another group of (20) healthy volunteers were selected as a control group and gray scale procedure was done for them in order to establish some preliminary data of the population.

Data collection: the data was collected using data sheet which include (age, history of diabetes or hypertension, gestational age, placenta site, IUFD, previous abortions due to diabetes or hypertension, amniotic fluid volume and fetal anomalies.)

Methods: 2Dimention Mindary ultrasound machine using gray scale type was used.

Protocol: The examination began with patient supine. First a fast survey is done to scan all uteri and its content, then a scan with details is done to evaluate and asses the heartbeat, gestational age, placenta site, amniotic fluid volume, presentation and asses fetal
weight and finally if there is any fetal anomalies is detected.

Measurements: There are two ways of measuring amniotic fluid, the first way is amniotic fluid index (AFI), second is the maximum pool depth (MPD). They have similar diagnostic accuracy; however (AFI) is commonly used. [6]

AFI is calculated by measuring maximum cord-free vertical pocket of amniotic fluid in four quadrants of uterus and adding then together. [6] Maximum Pool Depth is the maximum vertical measurement in any area. [6]

Data analyzed using SPSS to find the significant difference between the variables and the results presented in tables and graphs, significant correlation between the variables was represented in value($p=0.005$).

RESULTS:

Table (1) shows the distribution of age among u/s reports, N = 100

Age	Frequency	Percentage
20-25	28	28%
26-40	69	69%
41…and above	3	3%
Total	100	100%

*This table shown the age group (20-25) represented (28%) and the age group (26-40) represented (69%) as a highest percentage, age group (41 and above) represented (3%) represented (7%) as lowest percentage

Table (2) shows the incidence of poly, and oligohydramnios, N = 100

volume(AF) Amniotic Fluid	Frequency	Percentage
Normal AF	84	84%
Oligohydramnios	7	7%
Polyhydramnios	9	9%
Total	100	100

*This table shown the normal amniotic fluid represented (84%) as a highest percentage, polyhydramnios represented (9%) and oligohydramnios represented (7%) as lowest percentage

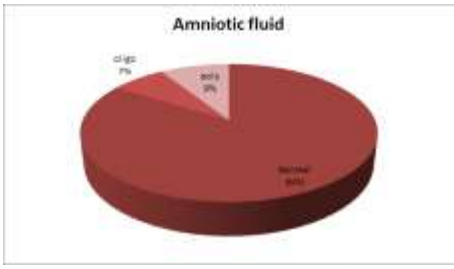

Figure (2) Pie graphs shows the percentage distribution of amniotic fluid volume

Table (2) explains the correlation between age groups and the amount of amniotic fluid

Age group	Normal AF in of total in Percentage & no		Oligohydramnios of total In percentage & no		Polyhydramnios of total In percentage & no		Percentage of patient in the age group Of Total no of patients
20-25	96.4%	27	0.0%	0	3.6%	1	28
26-40	81.2%	56	7.2%	5	11.6%	8	69
41…and above	33.3%	1	66.7%	2	0 .0%	0	3
Total		84		7		9	100

*This table explains the correlation between age groups and the amount of amniotic fluid. The normal AF in the age group (20 -25) and (26 – 40) represented higher percentage (96.4%) and (97.2%) respectively, the oligohydramnios represented higher percentage in age group (40 and above) with high significant relationship N=.000

DISCUSSION:

100 diabetic and hypertensive pregnant women had been examined using ultrasonography for assessing the pregnancy stats. Heart bear, gestational age, placenta site, intrauterine fetal death, fetal anomalies and amniotic fluid volume to detect any volume abnormalities.

Table (1) demonstrate the distribution of age group among 100 ultrasound reports, the age group (26 – 40) represented highest percentage (69%) and the age group (41 and above) represented lowest percentage (3%).

Table (2) and figure (2) shows the incidence of poly, and oligohydramnios, 9 of patients of the

study sample have a polyhydramnios (9%), 7 patients of sample have an oligohydramnios (7%), (84%) of samplehavenormalamnioticfluidvolume.

Table (3) table explains the correlation between age groups and the amount of amniotic fluid The normal AF in the age group (20 -25) and (26 – 40) represented higher percentage (96.4%) and (97.2%) respectively, the oligohydramnios represented higher percentage in age group (41 and above) with high significant relationship N=.000.

These results agree with a study reported by (N. RABI, 2017) [7] they said that: polyhydramnios is the term used to describe an excess accumulation of amniotic fluid. This clinical condition is associated with a high risk of poor pregnancy outcomes. The reported prevalence of polyhydramnios ranges from 0.2 to 1.6% of all pregnancies. The causes of polyhydramnios are fetal malformations and genetic anomalies (8–45%), maternal diabetes mellitus (5–26%), multiple pregnancies (8–10%), fetal anemia (1–11%).

Also agree with a study reported by (Lisa, 2017) [8] they said: The Amount of polyhydramnios attributable to diabetes may be less than previously reported that the rate of polyhydramnios is 8.5%. Patients with diabetes most commonly have mild polyhydramnios between 26 and 35.9 cm of fluid on a four-quadrant AFI.

A study written by (N. Idris,2010) [9], they reported that: The Influence of polyhydramnios on perinatal outcome in pregestational diabetic pregnancies reported that the incidence of polyhydramnios was 18.8%. Women withpolyhydramnioshadincreasedhemoglobinA1C (HbA1c)levelsthroughoutthepregnancy.

Another study reprted by (R.Scott,2001)[10], they said: Hanson Diabetes insipid us in pregnancy: A treatable cause of oligohydramnios mentioned that although rare, diabetes insipidus may present initially in pregnancy and should be considered in patients with oligohydramnios. Simple diagnosis wi th determination of 24-hour urine volume and serum electrolytes can identify this potentially reversible cause of oligohydramnios and poor obstetric outcome**.** Other study reported by (Joung.2004) [11] they reported: Early-Onset Oligohydramnios Complicated with Hypertension, reported that oligohydramnios is associated with increased perinatal morbidity and mortality. It may be due to a variety of conditions, including rupture of membranes, fetal urinary tract abnormalities such as posterior urethral valve, and prerenal abnormalities involving uteroplacental insufficiency may due to hypertensionandhyperthyroidism.

CONCLUSION:

Majority of women who have DM/HT undergo normal pregnancy and outcomes, but some of them might encounter complications with polyhydramnios, oligohydramnios, intrauterine fetal death, fetal congenital malformations and anomalies, and stillbirth. The incidence rate of these problems is increased with increasing maternalage.

Recommendation:

Pre-exciting hypertension and diabetes must be control to normal or closely to normal pre-conceptional to avoid the worse complications of them and consistently the worse outcome of them to mother or even to fetus.

Regular investigations should be done to detect any abnormal rates of high blood glucose or high blood pressure to avoid complication ofinducedhypertensionandgestationaldiabetes.

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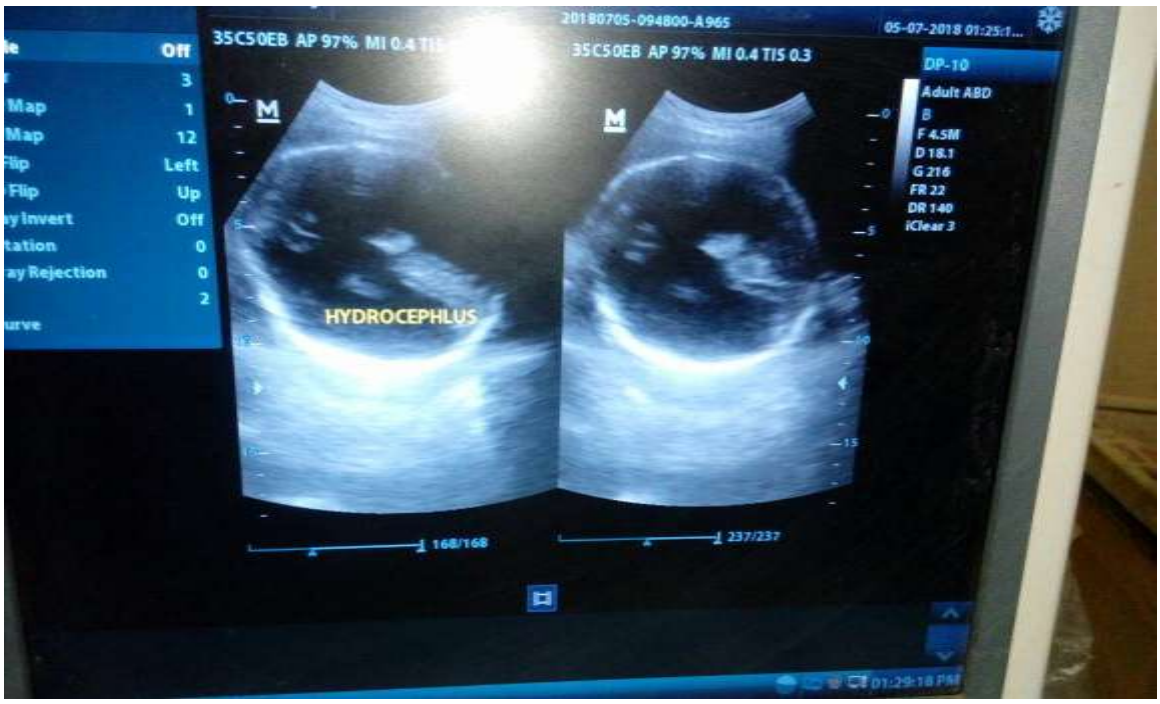
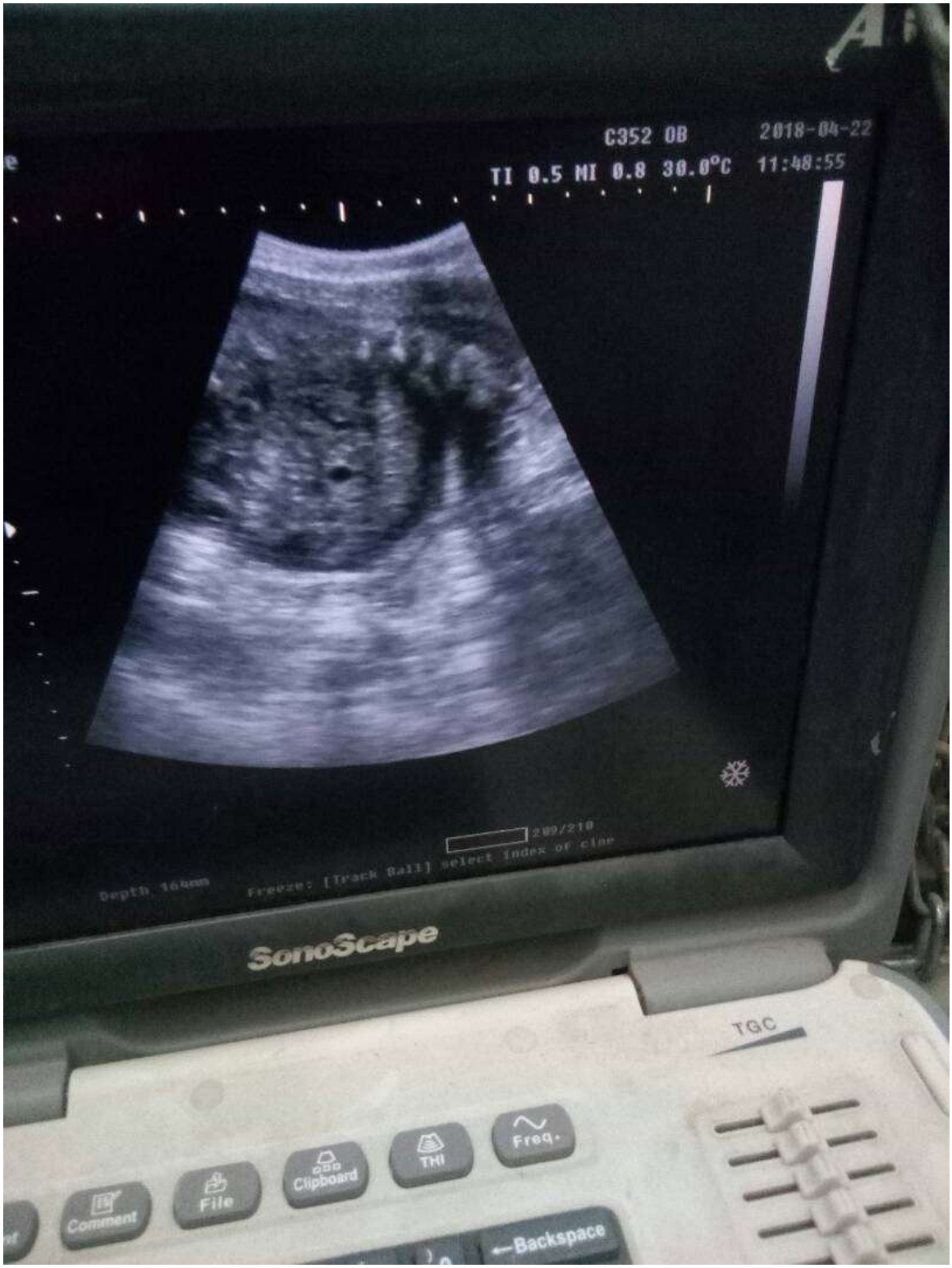


35 years old diabetic pregnant female patient with fetus with hydrocephalus. Gestational age is 33 weeks. The image is done by tow dimensional Mindary ultrasound machine in Medical Corp of Sudan on 5th of July 2018



A female 38 years old with hypertension with fetus with ascites. Gestational age is 27 weeks. The image is done by tow dimensional Mindary ultrasound machine in Medical Corp of Sudan on 22 of April 2018